Regulatory Guideline of

Registration of Locally Manufactured Medical Devices without International Quality Certificates

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Guide content

1. Introduction

This Guideline concerns the regulatory procedures for registering locally manufactured medical devices for factories holding ISO 13485:2016 certificate without CE certificate.

This decision shall be implemented in accordance with the following :

Registration of a medical device that was registered before during the validity of the CE certificate and the registration license is still valid

- Manufacturer submits a petition, after which the manufacturer will be granted a non-renewable 6-month period for production from the date of accepting the petition before submitting the registration file, provided that the factory applies GMP in accordance with the procedures of Central Administration of Operations (CAO).
- Production is permitted for a period of one year from the date of submitting the registration file, provided that the factory applies GMP in accordance with the procedures of Central Administration of Operations (CAO).
- If the requirements of re-registration file are not met upon the expiration of this period, production of the device and raw materials importation shall be ceased.

Registration of a sterile/non-sterile medical device that was registered before during the validity of the CE certificate and whose registration license has expired

- Production will be permitted for a period of one year from the date of submitting the registration file, provided that the factory applies Good Manufacturing Practices (GMP) in accordance with the procedures of Central Administration of Operations (CAO).
- If the requirements of the re-registration file are not met at the end of this period, production of the device and raw materials importation shall be ceased.

Registration of a non-sterile Class IIa, IIb and III medical device not registered before

- Trading will not be permitted until the completion of the registration procedures.
- - Factories are granted a period of one year to reconcile their situations from the issuance date of this guidelines to complete the registration procedures.
  - During the granted period, trading is the responsibility of the manufacturer, as the followed procedures before the issuance of the guidelines.
  - Medical devices that do not have an initial acceptance number will not be permitted to be traded after One year from the issuance of this guidelines.

Registration of a sterile medical device not registered before

- Trading will not be permitted until the completion of the registration procedures.

2. Definitions

1. Medical device: Any device, instrument, medium, machine, or application, including what is being implanted, or any laboratory reagent used in the laboratory, or electronic program, or substance or any other similar or related manufactured by the manufacturing company for the purpose of human use, whether used alone or in combination for one or more of the following medical purposes:

- Diagnosis, prevention, monitoring, treatment, alleviation of disease.
- Diagnosis, monitor, treatment, alleviation, compensation for an injury.
- Investigation, replacement, modification, or support of the anatomy or of a physiological process.
- Supporting or sustaining life.
- Control of conception.
- Disinfection of medical devices.
- Providing information by means of *in vitro* examination of specimens derived or taken from the human body.

Provided that it does not achieve its primary intended action by pharmacological, immunological, or metabolic means, in or on the human body, but which may be assisted in its intended function by such means.

2. Locally manufactured medical devices: The medical devices that are manufactured in factories inside the Arab Republic of Egypt.

3. non-sterile medical device: A medical device that is manufactured without being sterilized and is used as it is without sterilization or requires sterilization by the user before the use.

4. Factory: A local factory for medical devices.

5. Registration License: The EDA approval of the production, sale and promotion of a device inside the Arab Republic of Egypt after reviewing the device support guides.

6. Registration applicant: A local manufacturer, a scientific office for a local manufacturer.

7. Registration applicant representative: The authorized representative of the registration applicant to follow up all the works within the registration department.

8. Validation: A documentation process to verify that a process, procedure or activity will always lead to the expected results, and often includes qualification of systems and equipment, which is a requirement of GMP.

9. Step over benches: They are used in change rooms to form part of the change procedures, allowing personnel to change their clothing and footwear safely inside the cleanroom to minimize the risk of cross contamination

3. Related guidelines:

- Regulatory Guideline for registration of Imported and Locally Manufactured Medical Devices with International Quality Certificates
- Regulatory Guideline for Labelling Requirements for Medical Devices, Medical and Laboratory Equipment and *in vitro* Diagnostics, Components and Production Inputs
- Guideline for Using International Barcodes for All Medical Devices (UDI)

4. Classification of medical devices according to EU-MDD – Annex IX

a) Class I – Is (sterile) – Im (measurable), I (non-sterile)
b) Class II a
c) Class II b
d) Class III

- These requirements apply to medical devices' factories classified as class Is, IIa, IIb, and III.

- These requirements are not applied to medical devices' factories classified as I non-sterile, except for devices in pharmaceutical dosage form.

5. Technical requirements for medical devices factories

5.1 General conditions for a manufacturing site:

1. Factory must have obtained the necessary approvals from the competent authorities (Industrial Development Authority, Investment Authority, or General Authority for Suez Canal Economic Zone).
2. Factory must have its own independent entrances and exits.
3. Factory name must be shown in a visible signboard.
4. Height between the factory floor and the lower surface of the ceiling should not be less than 2.60 m.
5. Facility floor must be at the same level as the neighbouring land or higher, except when adequate precautions are taken to prevent water leakage into the factory, including creating a drainage network at an appropriate distance in order not to be a source of pollution. In all cases, manufacturing or storage steps must not be in a basement, with the exception of network services and utilities.
6. Manufacturing site must conform to the engineering drawings submitted to EDA. No modification may be made to the site before submitting a request for the required modification and conducting an actual inspection of the factory to ensure that health and technical requirements are met.
7. There must be a generator connected to the factory electrical circuit (for emergencies only).

Recommendation:

The committee recommends the presence of an uninterrupted power supply (UPS) device for operations or steps that require an uninterrupted power supply.

The committee also recommends submitting the following recommendations to the Industrial Development Authority (IDA):

1) The presence of a ground connection grid

2) When allocating land for the establishment of a medical devices factory, it should be taken into account that it is far from sources of infection and pollution and that it is in an environmentally appropriate area.

3) Spaces should be suitable for the number of workers.

5.2 Technical requirements of factory:

1. Separate bathrooms from changing rooms, with bathrooms being located before the gowning area;

2. Put a shoe rack (open stand) for street shoes and another for bathrooms;

3. Provide a ventilation source in bathrooms;

4. Place air curtains and insect zappers at all factory entrances (directly overlooking the street);

5. Regarding the primary gowning area, where street clothes are replaced with factory clothes and they are not unclassified, the following must be observed:

1) Separate street shoes from shoes worn inside the factory,
2) Separate workers', outer clothes from factory clothes, (de-gowning from gowning)
3) Have a ventilation source,
4) Provide lockers and a step-over bench (made of painted metal or stainless steel),
5) Designate a gowning area for women and another one for men,
6) Assign lockers for street clothes and others for factory clothes,
7) Do not put hand-washing basins near production areas, and a disinfectant for hand-washing, should be available
8) Have stout and smooth walls and floors with no visible joints,
9) Provide well, indirect ventilation (no fans), and good covered lighting,
10) Place stainless wire mesh nets over any ventilation openings.

5.2.1 Warehouses are divided into the following areas:

"According to the nature of the final product and production components"

- Receiving area

- Raw material storage area

- Packaging materials storage area

- Sampling area (classified as the same class as the production area if powders are used as raw materials) or an "inspection area" with controlled environmental conditions

- Weighing area (classified as Class D/ISO 8 in the case of using powers as raw materials)

- Rejection area, which must be tightly closed and secured

- Final product storage area

- Storage area for any raw materials or products that require special storage conditions.

Requirements for warehouses:

- Have a place covered with a canopy to ensure that the products or raw materials are not exposed to sunlight or any weather changes during loading to and from the warehouses;

- Have a receiving area that:

  - Have a main door with an "Interlocked" door system,
  - Is equipped with an air curtain and insect zappers,
  - Is ventilated like the whole warehouse.

- Well-ventilated;

- Temperature and humidity levels must be appropriate to the product nature,

- Monitor temperature and humidity through the factory's data loggers and thermal mapping,

- Floors must be strong,), for example but not limited to helicopter floors

- There should be rodent control system,

In case there is an emergency door, it must conform to the specifications of emergency doors in accordance with the requirements of the Civil Defence Agency, with the presence of an audible and flexible alarm system,

- There should be a fire extinguishing system and an alarm system in accordance with the requirements of the Civil Defence Agency,

- All warehouse doors must be tightly closed to prevent the entry of dust or insects,

- Have a wire mesh nets over any ventilation openings, with opaque glass to prevent direct sunlight,

- Sufficient lighting,

- No direct source of water in the storage area,

- Do not store directly on the floor non-flammable pallets or stands should be available. Storage should be 60 cm below the ceiling and 20 cm away from walls.

*** All the above-mentioned requirements must be met in case of there is an independent warehouse for final products**

5.2.2 Water treatment station:

"A water treatment station may only be set up in case a production line is licensed and needs treated water in its production"

Water treatment station consists of:

a. City water tank made of stainless-steel grade 316 L, or polyethylene or polypropylene,

b. A sand filter,

c. Carbon filter (activated granular carbon), at least one filter,

d. Two duplex softeners,

e. A storage tank for soft water,

f. Reverse osmosis or ion exchange resin or electro dialysis (for water purification),

g. UV lamp,

h. A 0.2-micron bacterial filter,

I. A stainless steel tank for storing purified water, provided that storage conditions are either above 85ºC or below 25ºC.

The following requirements must be observed at water treatment station:

- Water specification must be suitable for the nature of the medical device needed to be licensed;
- All rustable metals (iron, aluminium and copper) must be excluded;
- There should be a spray ball or vent filter in the purified water storage tank;
- Dead legs (ends) must be avoided in order not to be a source of pollution;
- There should be continuous water circulation (no stagnancy);
- Daily monitor water at multiple sampling points;
- All water storage tanks must be identified and water direction must be labelled
- In case of water is supplied an external body, the agreement with the supplier and water analysis certificate must be submitted.

5.2.3 Laboratories are divided according to the final product nature to:

A. Physiochemical laboratory

- Laboratory must be in a separate room, with its area being appropriate for the number of workers and the type and size of activity;

- Make sure that a suitable place is available to store chemicals in accordance with the storage requirements written on the containers;

- Ensure safety measures inside laboratory;

- Laboratory must be equipped with the necessary equipment in accordance with the requirements, provided that all devices are calibrated.

* In case of physicochemical examination of the product is carried out through manufacturing steps, the presence of a separate place for the laboratory may be overlooked and be considered part of the controlled area.

*Outsourcing is allowed.

B. Microbiological laboratory

- It should be in the controlled area;

- It should have a separate entry, divided from inside into physically distanced areas to prevent cross contamination according to the following laboratory activities:

1. Washing area,
2. Preparation area,

3. Incubators area, at least 2,
4. An autoclave for sterilization,
5. An autoclave for destruction,
6. A laminar air flow (LAF) unit with the following specifications:
   → Surrounding area shall be classified as the same as the production room, provided that the area shall not be less than Class D/ISO 8,
   → Preceded by an airlock for changing clothes classified D/ISO 8,
   → Floor shall be covered with a smooth material with technical specifications not less than that of epoxy without joints, and the junction point of walls and floors shall be curved,
   → Classification is not required for non-sterile devices,
   → There must be a dynamic pass box in the LAF room.

- All devices must be calibrated,

- There should be differential pressure meters,

- There should be temperature and humidity measuring devices,

- In the case of producing sterile pharmaceutical dosage forms, for example eye drops, the laboratory must meet the same conditions required for sterile pharmaceutical laboratories.

5.3 Sterilization

* Note: Regarding non-sterile medical devices (i.e., ready to be sterilized), the manufacturer's valid and approved method of sterilization shall be included inside the packages.

Outsourcing is permitted to carry out the sterilization process. The external manufacturer is required to be subject to inspection by EDA's Pharmaceutical Inspection Department, or that the manufacturer submits a pledge of their readiness to enable the department to enter the factory that performs sterilization at any time.

* In case of use of sterilization methods other than the following, each case will be studied individually.

A. In case of sterilization by gamma radiation

- The Medical Devices Factories Inspection Department verifies the existence of a contract between the factory and the Egyptian Atomic Energy Authority (EAEA).

B. In case of sterilization by steam

- An approved calibration certificate shall be available,

- Medical Devices Factories Inspection Department follows up the validation,

- If using a water station, the requirements for a water station must be followed,

- In the absence of a water station in the factory, a softener device is used at the water inlet of the autoclave for sterilization.

C. In case of sterilization by ethylene oxide/nitrogen dioxide

- An acceptance certificate from the device's manufacturer shall be available, including the acceptance test, operation qualification, OQ, and IQ (installation qualification),

- Conduct sterilization in a separate place,

- Provide a safe place to store gas cylinders (separate empty tubes from full ones),

- Use suitable pallets in accordance with the device operating manual released by the manufacturer.

The aeration room should:

a. Be proportional in area to the size of the sterilization device,

b. Have temperature and humidity measurement meters,

c. Have a source of heating (heater) in case of need,

d. Well ventilated.

Regarding production areas, the following should be observed in accordance with the product nature:

- For sterile medical devices: Production and packaging take place inside the clean room;

- For non-sterile medical devices and ready for sterilization before use: Production inside a classified area is not required, and packaging takes place inside the clean room;

- Medical devices produced and used non-sterile: Production and packaging are not required to take place in a classified area (unless the manufacturing specification states so);

- In case any of the manufacturing stages or production components requires special conditions, these conditions must be taken into account.

5.4 Controlled room

It is the area in which the unpackaged and unsterilized product is prepared, and the following conditions should be observed:

- The controlled room should be separate (not used as a corridor);

- Designate a place for changing clothes before entering the controlled room;

- Designate a place for cleaning and removing the outer package of raw materials before being taken to the controlled room, and the place should contain a ventilation source and an exhaust fan;

- It should be well ventilated, with temperature not exceeding 30°C, and fans are not allowed;

- Put a temperature and humidity meters inside the controlled room, with temperature not exceeding 30°C and humidity 65%;

- Floors must be strong, smooth and clean – that is to be, for example, tiles or epoxy;

- Designate a place to store the Molds attached to the controlled room when needed;

- Make sure when taking the product ((i.e., a classified airlock or a dynamic pass box)) out of the controlled room that it enters the clean room safely (place it inside a double bag) for example (through a classified airlock or a dynamic pass box) or be stored in intermediate store that conforms to the requirements for sound storage.

5.5 Clean room

- Should be preceded by a secondary gowning room and a de-gowning room, and then pass by a step-over bench to wear the clean room gowning;

- Doors should be interlocked;

- Secondary gowning room should be Class D/ISO 8;

- Pressure should be cascading by having pressure differential meters. The pressure differential between adjacent cleanrooms or clean zones of different cleanliness level should lie typically in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintended cross-flows due to turbulence i.e.:

- Between rooms of different grades should have pressure differential of approximately 10-15Pa;

- Doors open in the cleaner direction that has more pressure;

- Floors must be strong and smooth, such as epoxy or vinyl;

- Walls must be smooth and the connection between walls and floors must be curved;

- Temperature should not exceed 22°C and humidity 65%;

- In case of printing on the product, the printing must take place within the clean room; in case of using inks, the area where the inks are used must be physically separated;

- In case of printing outside the clean room, justification shall be provided;

- Raw materials enter through the aerated pass box or classified airlock;

- Install pressure differential meters at all doors and pass boxes of the clean room;

- Supply grills should be in the ceiling and the return grills in the side walls 50 cm above the floor;

- Height between the floor and the ceiling should not be less than 2.60 m;

- Air change rate ranges between 15-20 per hour.

Air handling unit HVAC system

<u>It should not be applied to products not manufactured or packaged in a clean room</u>

- There should be an air handling unit including a prefilter, a bag filter, and an HEPA (high-efficiency particulate air) filter;

- There should be a pressure differential meter for the prefilter and bag filter, and another one before and after the HEPA filter;

- The air handling unit should be placed in the technical room or be covered with a canopy. The floor should be tiled and the area around is clean.

Scope of application

- These requirements have been set for the factories that will be established and licensed for the first time.
- For factories that had been licensed before the requirements were issued, they are given a period of six months to reconcile their situation, which can be extended for another six months if the factory submits a request to extend the period.
- In case of the factory does not implement any of the previous requirements due to the nature of manufacturing the medical devices, the factory must submit studies supported by justification and reference that will be presented to the Supreme Inspection Committee for evaluation.
- Manufacturers of medical dosage-form devices are subject to GMP for pharmaceutical preparations in accordance with WHO.

6. Procedures and rules governing the registration of the locally manufactured medical devices without international quality certificate:

Pre-registration procedures:

1. The factory shall obtain a technical operation license (data certificate) from the General Administration of Licensing in the Central Administration of Operations. After the issuance of the aforementioned certificate, manufacturer shall head to the Medical Devices Inspection Department in the Central Administration of Operations for the following:

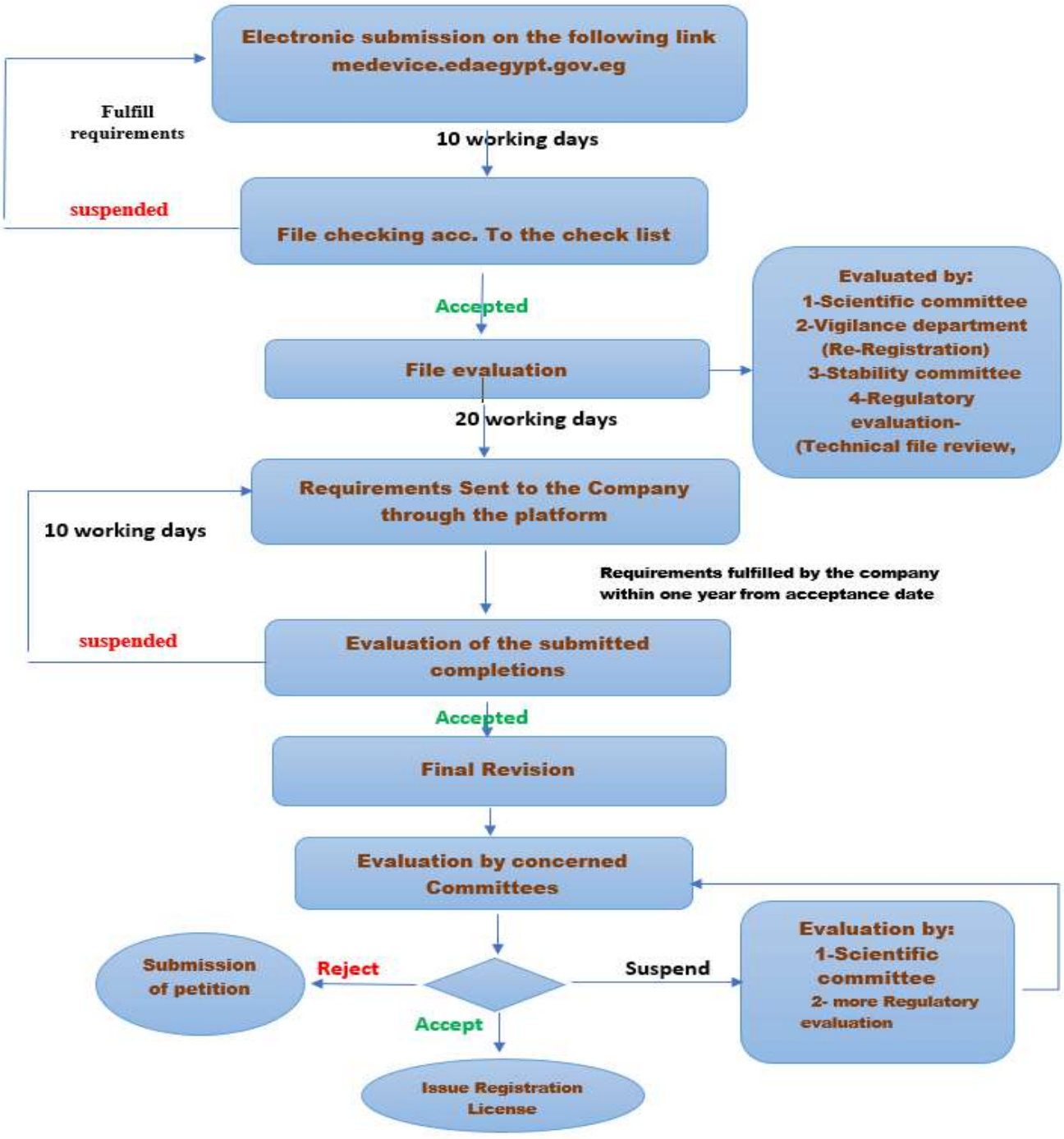
- Ensure that the factory is applying the technical requirements of the manufacturing site within 20 working days,
- Manufacturer is informed of the required corrective measures,
- Manufacturer completes the technical requirements for the manufacturing site within a maximum of 120 working days,
- If the 120 working days have expired and the manufacturer has not completed the corrective measures, the manufacturer has the right to apply for an additional grace period of another 40 working days, after which an inspection report will be issued stating that the factory applies the GMP regarding the procedures of the Central Administration of Operations

2. Production of pilot batch is permitted, provided that this batch is never traded in the local market, and the registration procedures and studies required for it are completed.

3. Manufacturer applies online to register a medical device without international quality certificates on the electronic platform at: http://medevice.edaegypt.gov.eg

4. Medical Devices Inspection Department withdraws samples from the pilot batch for analysis in the EDA's laboratories or any other body approved by EDA and chosen by the competent department. The registration applicant is obligated to submit the analysis file to EDA containing the documents and attachments required for the analysis file.

Flow Chart of Registration of locally manufactured Medical Devices without quality certificates



6.1 Procedures for receiving registration file

1. The Reception pharmacist will meet with the registration applicant to add the name of the medical device to the payment receipt of the fees and services.

The medical device registration application fees are collected for the fees category mentioned in the executive regulations of the EDA establishment law issued by Prime Minister's Resolution No. 777 of 2020 and for the services in accordance with EDA chairman's decision in this regard.

2. Company applies online at the following link: http://medevice.edaegypt.gov.eg

3. Company will receive a reply through the platform within 10 working days from the date of submitting the request.

- If the application is accepted: The request will be directed to the reviewing pharmacist who studies the request and sends the requirements to the company to complete the procedures within 20 working days,
- If the application is suspended until completion: The application is suspended if any of the documents are not completed according to the announced checklist for a maximum period of 90 working days, after which the application will be rejected. If the documents are complete after the aforementioned period, the fees of the service must be paid in full.

When the company fulfils the required documents within 90 working days, the application may be completed on the platform using the same application number submitted previously.

- If the application is rejected: the application will be rejected in case the medical device data in application doesn't match with that mentioned in payment receipt or the application is not relevant to the administration to which the application is directed.

6.2 Procedures for evaluating medical device registration file

- The file shall be reviewed and the needed requirements shall be identified on the platform within 20 working days from the date of acceptance of the file;

- Medical device vigilance procedures are followed as detailed in Clause 6.4;

- Medical device shall be to presented to the specialized scientific committee to be evaluated;

- Specialized scientific committee for stability studies & Biocompatibility evaluation procedures shall be followed to evaluate the safety mentioned in Clause 6 of the Regulatory Guidelines for the Procedures for Registering Imported and Local manufactured Medical Devices with International Quality Certificates.

6.3 Procedures for completing the medical device registration file

- Completions of the registration file are submitted on the platform and a receipt for payment of the completion fees is attached;

- Completions submitted by the manufacturer shall be reviewed within 10 working days;

- If a calendar year has elapsed from the date of acceptance of the registration file and the factory has not completed the file, the registration application shall be considered cancelled;

In case of non-sterile medical devices: The applying company shall be given a period of 6 months from the date of submitting the registration file for trading after the initial evaluation of the file.

6.4 Medical devices vigilance procedures

6.4.1 Medical devices vigilance requirements

** A Class I and Class IIa medical device submitted for re-registration and no regulatory procedures have been taken.

Factories must submit the commitment (attached) to the General Administration for registration, and a transfer letter will be issued for them to follow with the vigilance Administration.

** A Class I and Class IIa medical device submitted for re-registration and regulatory procedures have been taken over the three years that had preceded the application date.

• Factories shall go to the vigilance Administration pursuant to a transfer letter from the General Administration for Registration to submit the documents required to evaluate the safety within the re-registration/variables framework, which does not include a summary of marketing history (SMH).

• Submit the required commitment (attached), to be sent to the Medical Devices Registration Department.

** Class IIb and III medical device submitted for re-registration

• Factories are instructed to go to the Medical Devices Safety Department according to a transfer letter from the General Administration for Registration to submit the documents required for safety evaluation within the re-registration/variation framework, which includes SMH.

• Submit the required commitment (attached), to be sent to the Medical Devices Registration Department.

6.4.2 vigilance requirements for companies (not linked to registration)

1-In case of a request for registration/re-registration, the local manufacturer is obligated to submit a commitment of the presence of a medical devices vigilance system and the follow-up of all its activities and requirements in accordance with the guidelines for the medical devices vigilance system with the Medical Devices Safety Department at the (Egyptian Pharmaceutical Vigilance Center)

2-The local manufacturer is obligated to report any recall, FSN (field safety notice) or FSCA (field safety corrective action) procedures that take place globally or any incidents that are monitored in the Arab Republic of Egypt to the Medical Devices Safety Department at the Egyptian Pharmaceutical Vigilance Centre, according to the time periods specified in the guidelines for the medical devices vigilance system.

3-Companies are obligated to appoint a vigilance officer or add his duties to a supervisory affairs officer and submit his nomination letter to the Medical Devices Safety Department.

4-Companies are obligated to pay for the services when submitting their files to the Medical Devices Safety Department.
Companies comply with all applicable regulatory rules and guidelines and their amendments regarding safety requirements (if any).

6.5 Issuance of registration license

A registration license for the local medical devices without quality certificates shall be issued and is valid for a period of five years from the date of issuance of the registration license. Factories are obligated to analyse the first three batches produced after the issuance of the registration license, provided that the batch will not be released until the conformity result of the analysis is issued.

6.6 Re-registration procedures

- Medical devices are re-registered every five years based on an application submitted to the Central administration of Medical Devices during the first three months of the last year of the valid registration license.

- Applicant is obligated to submit the re-registration file according to the list of required documents.

- Fees for services are collected in accordance with a decision of EDA chairman in this regard.

- The re-registration procedures shall be presented to the specialized scientific committee to assess the medical device.

Specialized scientific committee for stability studies & Biocompatibility evaluation

- Medical device re-registration shall not be submitted to the Specialized scientific committee for stability studies & Biocompatibility evaluation if no modification has occurred in the raw materials of the package and if a Real Time Stability Study is submitted for the first time of registration or during the registration license validity.
- If the Real Time Stability Study is not submitted upon first registration or within the period of registration license validity., device will be assessed upon re-registration.
- In case of a change in the raw materials, the biocompatibility study is re-assessed by Specialized scientific committee for stability studies & Biocompatibility evaluation.
- If the sterilization method is changed, the following shall be re-assessed by the specialized scientific committee for stability studies & Biocompatibility evaluation:
  - New stability study including sterilization validation only and re-evaluation of biological risk assessment.
- In case of a change in the packaging dimension or packaging material, the following shall be re-assessed by Specialized scientific committee for stability studies & Biocompatibility evaluation
  - New stability study including packaging validation only and re-evaluation of biological risk assessment.
- If the shelf life and/or storage conditions are changed, the following shall be re-assessed by specialized scientific committee for stability studies & Biocompatibility evaluation:
  - New stability study and re-evaluation of biological risk assessment.

- Applicant is obligated to complete the re-registration procedures within the last year of the registration license production and trading is permitted during this year. If the requirements of the final file are not met at the end of this period, the production or importation of raw materials shall be ceased, and the application shall be considered cancelled.

7. General requirements

Manufacturer should:

- Obtain ISO 13485:2016 Certificate;

- Print all data and registration number on the package according to the Regulatory Guideline for Labelling Requirements for Medical Devices, Medical and Laboratory Equipment and in Vitro Diagnostics, Components and Production Inputs.

- Import raw materials used in the medical device after obtaining approval from the Central administration of Medical Devices or submitting evidence of purchasing it locally.

If the factory is located in a free zone, manufacturer should:

- Provide evidence of importing raw materials used in the medical device or purchasing them locally;

- Make no change to the medical devices except after obtaining the approval of the Central administration of Medical Devices according to the applicable procedures in accordance with the type of change, otherwise the registration license will be cancelled;

- Make no change to the critical component's suppliers of raw materials except after obtaining the approval from the Central administration of Medical Devices to re-evaluate the device supplier, otherwise the registration license will be cancelled;

- Apply Vigilance System;

- Adhere to vigilance requirements;

- Print on the device the following QR code, which shows the internet link for reporting to EDA any problems to patients or users or problems related to use or quality.

8. Annexes

Annex I: List of documents for registering locally manufactured medical devices without quality certificates

Annex II: Technical requirements that must be met by a medical devices factory

Annex III: vigilance requirements for medical devices

Annex I

List of documents for registering locally manufactured medical devices without quality certificates

First, documents required by applicant

1	Fee and services payment receipt
3	Manufacturer's commitment to implement safety mechanisms
4	Original delegation letter issued by manufacturer, approved by the board chairman, with bank authentication of the signature of the delegated person in charge of dealing with the Central administration of Medical Devices.
5	**Local factories** - Commercial record - Tax card - Operating license issued by the General Authority for Industrial Development - Technical operating license (data certificate) issued by the Central Operations) Administration **Free zone factories** - Commercial record - Tax card - License issued by the General Authority for Investment and Free Zones to practice activity under the free zone system - Technical operating license (data certificate) issued by the Central Operations Administration

Second, Technical documentation

REGULATORY REQUIREMENTS	
1. Administrative information	
1.1	Name of manufacturer
1.2	Address of manufacturer
1.3	Name and Address of any associated manufacturing sites
1.4	Statement of legal liability (designing a from for the manufacturers to follow) (attached)
1.5	License of manufacturing no or (IDA)/ Investment License (attached)
1.6	Data certificate no. (attached)
1.7	Industrial registry no.(attached)
1.8	Latest commercial card (attached)
1.9	Name of authorized contact person, authorized person delegation letter (attached) and name of person responsible for regulatory compliance a contact detail
1.10	Tel
1.11	Fax
1.12	E-mail
1.13	Web address
1.14	Declaration of conformity/letter of declaration according to the adopted regulation (attached)
1.15	Certificates ISO 13485:2016 from accredited certification bodies (attached)
1.16	List of the harmonized standards, Common Specifications (CS) and other standards relevant for the product (attached)
1.17	Qualification of person/s (CV's) and or team perform the clinical evaluation report, risk management and biological evaluation reports

2. Product description	
2.1	Product name
2.2	Trade name
2.3	Intended use and performance claims comply with IFU
2.4	Definition of the intended patient population and medical condition for which the device is intended
2.5	Adopted regulation, Applicable directive
2.6	Classification of the device and accessories (according to the adopted regulation +equivalent classification in the European regulation)
	3. Manufacturing
3.1	General description of the manufacturing processes
3.2	Manufacturing Process Validation (if applicable)
3.3	Work environmental conditions in the manufacturing process (according to device nature) and clean room validation if applicable
3.4	Description of sterilization process
3.5	Contracts with manufacturer/subcontractor
3.6	Critical supplier list, agreements, and certificates copy
4. Product specifications	
4.1	General description of the product and variations/definition of the product
4.2	Description of accessory equipment, adapters, equipment and other devices used with the products
4.3	Composition of the product, components used, list of parts
4.4	Material specifications/ substance used
4.5	Material safety data sheets (MSDS)/ Component certificate of compliance
4.6	Construction documents, technical drawings and product photo
4.7	Functional description of the major components
4.8	Specifications of the packaging material
4.9	Declaration Letter for the packaging (to declare that the packaging material is compatible with sterilization method, storage conditions and transportation conditions)
4.10	Indications and contraindications of the product
4.11	Final product release criteria
5. Biological compatibility	
5.1	Compliance with ISO 10933-1 (Biological evaluation assessment report) and chemical characterization
5.2	Laboratory accreditation copy
5.3	Justification for any deviations
5.4	Biological evaluation report and summary
6. Quality assurance measures	
6.1	Test plan /protocol (incoming materials, raw material, in-process contain, end-control)
6.2	Test report /analysis certification (test result) (incoming materials, raw material, in-process contain, end-control)
6.3	Batch documentation, product traceability
6.4	Documents master list
7. Information supplied by the manufacturer	
7.1	Languages (English/Arabic)
7.2	Product labelling (evidence of compliance with ISO 15223)
7.3	Additional documentation (IFU, user guide, service book, information for patient)
7.4	Warning /special precautionary measures/Contra-Indications
7.5	Symbols used

7.6	Storage/transport/disposal
7.7	Brochures, marketing material (matched with intended use and claims), if the brochures and marketing material via website link must be submitted
	8. Software (if applicable)
8.1	Development methodology
8.2	Concept of software life-cycle
8.3	URS (User requirements specifications)
8.4	Functional Specifications or software specifications (FS)
8.5	Software module test (test plan, test reports, SOP)
8.6	Information about the used programming standard (which guidance was applied)
	9. Product verification (performance testing) (according to manufacturing standards)
9.1	Essential Requirements compliance and checklist
9.2	Performance tests complies with product standard (through third party, accredited national or international lab or at facility under supervision of the inspection team including NODCAR member)
9.3	Electrical safety
9.4	Packaging validation
9.5	Sterilization validation, subcontractors' contract if applicable and certificates
9.6	Shelf-life tests (in-house or outsourced) including packaging integrity, device performance and biological safety
9.7	Bio stability test (influence of the biological substance onto the product – implantable devices). Rephrasing: Life time of the product (performance of the device through its life time in human body)
9.8	Software verification and validation (EN 60601-1-4) (Through accredited lab)
9.9	Electromagnetic compatibility test report (EN 60601-1-2)
9.10	Evidence of compatibility with other medical devices/medicines/preparation
9.11	Transportation and handling validation reports
9.12	Usability study
	10. Evidence of Compliance with ISO14971
10.1	Risk management plan, analysis and control
10.2	Production and post-production information and risk benefit analysis, undesirable side effects, etc. Risk Management assessment should be conducted for the entire life-cycle of the device (from initial design concept up to and including device disposal)
	11. Clinical evaluation assessment
11.1	Clinical evaluation report (CER) –all protocols and reports quoted in the clinical report, copies of the publications quoted in the clinical report
11.2	Clinical investigation or justification from manufacturer for not implementing clinical investigation
	12. Post Marketing
12.1	Post marketing plan (reflecting the residual risks resulted in the benefit/risk analysis) to be submitted annually
12.2	Copies from last complaints, incident, recall records and reports last 5 years
12.3	Post marketing surveillance (PMS) report
	13. Regulatory procedures
13.1	Copies from all regulatory procedures (Clinical evaluation, vigilance, change control, recall and advisory notice, etc.)

Annex II

Technical requirements that must be met by a medical devices factory

1. Facilities & Utilities	According to product specifications

Workers Entry Area

1. Separate bathrooms from changing rooms, with bathrooms being located before the dressing area;
2. Put a shoe rack (open stand) for street shoes and another for bathrooms;
3. Provide a ventilation source in bathrooms;
4. Place air curtains and insect zappers at all factory entrances (directly overlooking the street);

Gowning Area: An unclassified area where street clothes are replaced with factory clothes, with the following should be observed

1. Separate street shoes from shoes worn inside the factory,
2. Separate workers' outer clothing from factory clothing (de-gowning from gowning),
3. Have a ventilation source,
4. Provide lockers and a step-over bench (made of painted metal or stainless steel),
5. Designate a gowning area for women and another for men,
6. Assign lockers for street clothes and others for factory clothes,
7. Do not put hand-washing basins near production areas, and a disinfectant for hand-washing should be available,
8. Have stout and smooth walls and floors with no visible joints,
9. Provide well, indirect ventilation (no fans), and good covered lighting,
10. Place stainless wire mesh nets over any ventilation openings.

Warehouses

They are divided into the following areas:

A. Receiving area
B. Raw material storage area
C. Packaging materials storage area
D. Sampling area (classified as the same class as the production area if powders are used as raw materials) or an "inspection area" with controlled environmental conditions
E. Weighing area (classified as Class D/ISO 8 in the case of using powders as raw materials)
F. Rejection area, which must be tightly closed and secured
G. Final product storage area
H. Storage area for any raw materials or products that require special storage conditions.

- The above division into 8 areas may not be observed according to the nature of the final product and production components
- The temperature should not exceed 30°C and humidity 65% unless the device specifications state otherwise, provided that the temperature and humidity be suitable to the nature of the product.

Requirements for warehouses

1) Have a place covered with a canopy to ensure that the products or raw materials are not exposed to sunlight or any weather changes during loading to and from the warehouses;
2) Have a receiving area that:
   - Have a main door with an "Interlocked" door system,
   - Is equipped with an air curtain and insect zappers,
   - Is ventilated like the whole warehouse.
3) Well-ventilated;
4) Temperature and humidity levels must be appropriate to the product nature,
5) Monitor temperature and humidity through the factory's data loggers and thermal mapping,

6) Floors must be strong, such for example but not limited to helicopter floors,
7) There should be rodent control system,
8) In case there is an emergency door, it must conform to the specifications of emergency doors in accordance with the requirements of the Civil Defence Agency, with the presence of an audible and flexible alarm system,
9) There should be a fire extinguishing system and an alarm system in accordance with the requirements of the Civil Defence Agency,
10) All warehouse doors must be tightly closed to prevent the entry of dust or insects,
11) Have a wire mesh nets over any ventilation openings, with opaque glass to prevent direct sunlight,
12) Sufficient lighting,
13) No direct source of water in the storage area,
14) Do not store directly on the floor if, non-flammable pallets or stands should be available. Storage should be 60 cm below the ceiling and 20 cm away from walls.

Note:

If there is an independent warehouse for final products, all the above-mentioned requirements must be met.

Water treatment station

A water treatment station may only be set up in case a production line is licensed and needs treated water in its production

Water treatment station consists of:

a. City water tank made of stainless grade 316 L, or polyethylene or polypropylene,
b. A sand filter,
c. Carbon filter (activated granular carbon), at least one filter,
d. Two duplex softeners,
e. A storage tank for soft water,
f. Reverse osmosis or ion exchange resin or electro dialysis (for water purification),
g. UV lamp,
h. A 0.2-micron bacterial filter,
i. A stainless steel tank for storing purified water, provided that storage conditions are either above 85^{o}C or below 25^{o}C.

The following requirements must be observed at the water treatment station:

- Water specification must be suitable for the nature of the medical device needed to be licensed;
- All rustable metals (iron, aluminium and copper) must be excluded;
- There should be a spray ball or vent filter in the purified water storage tank;
- Dead legs (ends) must be avoided in order not to be a source of pollution;
- There should be continuous water circulation (no stagnancy);
- Daily monitor water at multiple sampling points;
- All water storage tanks must be identified and water direction must be labelled
- In case of water comes from an external source, the contract signed with the provider and water analysis certificate must be submitted.

Laboratories (physiochemical laboratory & Microbiological laboratory)

Manufacturer is committed to establish laboratories in accordance with the nature of the final product and the tests required to be conducted on it.

A. Physiochemical laboratory

Outsourcing is allowed in case there is no laboratory in the factory.

- Laboratory must be in a separate room, with its area being appropriate for the number of workers and the type and size of activity;
- Make sure that a suitable place is available to store chemicals in accordance with the storage requirements written on the containers;
- Ensure safety measures inside laboratory;
- Laboratory must be equipped with the necessary equipment in accordance with the requirements, provided that all devices are calibrated.
- In case of physicochemical examination of the product is carried out through manufacturing steps, the presence of a separate place for the laboratory may be overlooked and be considered part of the controlled area.

B. Microbiological laboratory

1. It should be in the controlled area;
2. It should have a separate entry, divided from inside into physically distanced areas to prevent cross contamination according to the following laboratory activities:

a. Washing area,
b. Preparation area,
c. Incubators area, at least 2,
d. An autoclave for sterilization,
e. An autoclave for destruction,
f. A laminar air flow (LAF) unit with the following specifications:

- Surrounding area shall be classified as the same as the production room, provided that the area shall not be less than Class D/ISO 8,
- Preceded by an airlock for changing clothes classified D/ISO 8.
- Floor shall be covered with a smooth material with technical specifications not less than that of epoxy material without joints, and the junction point of walls and floors shall be curved,
- Classification is not required for non-sterile devices,
- There must be a dynamic pass box in the LAF room, and all devices must be calibrated,
- There should be differential pressure meters,
- There should be temperature and humidity measuring devices,
- In the case of producing sterile pharmaceutical dosage forms, for example eye drops, the laboratory must meet the same conditions required for sterile pharmaceutical laboratories.

Sterilization

- Outsourcing is permitted for the sterilization process. The outsource is subjected to inspection by EDA's Pharmaceutical Inspection Department, or the manufacturer commit to comply to the inspection process by EDA Pharmaceutical Inspection Department whenever it is stated.
- Regarding non-sterile medical devices (i.e., ready to be sterilized by the user's ready-to-be-sterilized), the manufacturer's valid and approved method of sterilization shall be included inside the packages.

If there is sterilization method other than the following, each case will be studied individually.

A. Gamma radiation sterilization

The Medical Devices Factories Inspection Department verifies the existence of a contract between the factory and the Egyptian Atomic Energy Authority (EAEA).

B. Steam sterilization
- An approved calibration certificate shall be available,
- Medical Devices Factories Inspection Department follows up the validation,
- If using a water station, the requirements for a water station must be followed. In the absence of a water station in the factory, a softener device is used at the water inlet of the autoclave for sterilization.

C. Ethylene oxide/nitrogen dioxide sterilization
- An acceptance test certificate from the device's manufacturer shall be available,
- OQ (operational qualification),
- IQ (installation qualification),
- Conduct sterilization in a separate place,
- Provide a safe place to store gas cylinders (separate empty tubes from full ones),
- Use suitable pallets in accordance with the device operating manual released by the manufacturer.

The aeration room should:
- Be proportional in area to the size of the sterilization device,
- Have measure temperature and humidity meters,
- Have a source of heating (heater) in case of need,
- Well ventilated.

Controlled area

It is the area in which the product is prepared unpackaged and unsterilized, and the following conditions should be observed:

Regarding production areas, the following should be observed in accordance with the product nature:

- For sterile medical devices: Production and packaging take place inside the clean room;
- For non- sterile medical devices and ready for sterilization before use: Production inside a classified area is not required, and packaging takes place inside the clean room;
- Medical devices produced and used non-sterile: Production and packaging are not required to take place in a classified area (unless the manufacturing specification states so);

In case any of the manufacturing stages or production components requires special conditions, these conditions must be taken into account.

Controlled room

1. It should be separate and not used as a corridor;
2. If water is used in the production process, its entry and exit must be in a closed path
3. Designate a place for changing clothes before entering the controlled room;
4. Designate a place for cleaning and removing the outer package of raw materials before being taken to the controlled room, and the place should contain a ventilation source and an exhaust fan;
5. it should be well ventilated, with temperature not exceeding 30°C, and fans are not allowed;
6. Put a temperature and humidity meters inside the controlled room, with temperature not exceeding 30°C and humidity 65%;
7. Floors must be strong, smooth and clean – that is to be, for example, tiles or epoxy;
8. Designate a place to store the Molds attached to the controlled room when needed;
9. Make sure when taking the product out of the controlled room that it enters the clean room safely (place it inside a double bag) for example through (a classified airlock or a dynamic pass box) or be stored in intermediate store that conforms to the requirements for sound storage.

Clean room

In case of printing outside the clean room, justification should be provided, so that:

1. It should be preceded by a secondary gowning room;
2. It should be preceded by a de-gowning room and then pass by a step-over bench to wear clothing;
3. Door should be interlocked;
4. Secondary gowning room should be Class D/ISO 8;
5. It should have cascading pressure by installing pressure differential meters, so that:
    - The pressure differential between adjacent cleanrooms or clean zones of different cleanliness level should lie typically in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintended cross-flows due to turbulence.
6. Doors should open in the cleaner direction that has more pressure;
7. Floors should be strong and smooth; it could be made of epoxy or vinyl;
8. Walls should be smooth, and the connection between walls and floors must be curved;
9. Temperature should not exceed 22°C and humidity no more than 65%;
10. In case of printing on the product, the printing process should take place within the clean room; in case of using inks, the area where the inks are used must be physically separated;
11. In case of printing outside the clean room, justification should be provided;
12. Pressure differential meters should be installed at all doors and pass boxes of the clean room;
13. Supply grills should be installed in the ceiling and the return grills in the side walls 50 cm above the floor;
14. Height between the floor and ceiling should not be less than 2.60 m;
15. Number of air changes should range between 15-20/h.

Air handling unit HVAC system

It is not applicable for products not manufactured or packaged in a clean room

1. There should be an air handling unit including a prefilter, a bag filter, and an HEPA (high-efficiency particulate air) filter;
2. There should be a pressure differential meter for the prefilter and bag filter, and another one before and after the HEPA filter;
3. The air handling unit should be placed in the technical room or be covered with a canopy. The floor should be tiled and the area around is clean.

Annex III

Safety requirements for medical devices

[COMPANY NAME]

(Date)

Manufacturer's endorsement about safety of medical devices

Declaration (1)

For MDs Class I and IIa

Dear Head of the Central Administration of Medical Devices,

Dear Head of General Administration of the medical Device Registration,

For the following medical devices applied for registration/re-registration/variation of marketing authorization in the Arab Republic of Egypt:

- Medical Device Name:

- Medical Device Models/Codes:

- (Company) undertakes that the medical device applied for registration/re-registration/variation, which will be marketed in the Arab Republic of Egypt, has not received any **recalls**, **FSNs**, or **FSCAs** in respect of (Models/Codes No., Lot/Batch No., or Serial No.), in the past (3) three years before the application for registration/re-registration/variation.
- (Company) undertakes that in case of any **recalls**, **FSNs**, or **FSCAs raised after submitting the registration/re-registration/variation application file and before granting the marketing authorization of the medical device, those recalls, FSNs or FSCAs concerning the safety of the medical device** in respect of (Models/
- Codes No., Lot/Batch No., or Serial No.) will be communicated to the Medical Device Safety Department (MDSD - EPVC), by (Agent)- the company's agent in the Arab republic of Egypt.
- (Company) undertakes that since granting the marketing authorization of the medical device and during the marketing stage, (Company) will be obliged to communicate any incidents (MIRs), periodic safety reports (PSR), or regulatory actions (including but not limited to **recalls**, **FSNs**, or **FSCAs** to the Medical Device Safety Department (MDSD - EPVC) by (Agent) – the company's agent in the Arab Republic of Egypt, this is according to the Egyptian Guidelines for Medical Device Vigilance System.
- (Company) undertakes that there is a vigilance system in place, oversights the vigilance system of the (Agent) – the company's agent in the Arab Republic of Egypt, and makes sure that (Agent) meets all vigilance requirements (in reference to the Egyptian Guidelines for Medical Device Vigilance System), and communicates them with the Medical Device Safety Department (MDSD - EPVC).

Signature

Title

(Date)

[COMPANY NAME]

(Date)

Manufacturer's endorsement about safety of medical devices

Declaration (2)

For MDs Class IIb and III (I, IIa with Regulatory Action)

Dear Head of the Central Administration of Medical Devices,

Dear Head of General Administration of the medical Device Registration,

For the following medical devices applied for registration/re-registration/variation of marketing authorization in the Arab Republic of Egypt:

- Medical Device Name:

- Medical Device Models/Codes:

- (Company) undertakes that in case of any **recalls**, **FSNs**, or **FSCAs raised after submitting the registration/re-registration/variation application file and before granting the marketing authorization of the medical device, those recalls, FSNs or FSCAs concerning the safety of the medical device** in respect of (Models/Codes No., Lot/Batch No., or Serial No.) will be communicated to the Medical Device Safety Department (MDSD - EPVC), by (Agent) - the company's agent in the Arab republic of Egypt.
- (Company) undertakes that since granting the marketing authorization of the medical device and during the marketing stage, (Company) will be obliged to communicate any incidents (MIRs), periodic safety reports (PSR), or regulatory actions (including but not limited to **recalls**, **FSNs**, or **FSCAs** to the Medical Device Safety Department (MDSD - EPVC) by (Agent) - the company's agent in the Arab Republic of Egypt, this is according to the Egyptian Guidelines for Medical Device Vigilance System.
- (Company) undertakes that there is a vigilance system in place, oversights the vigilance system of the (Agent) - the company's agent in the Arab Republic of Egypt, and makes sure that (Agent) meets all vigilance requirements (in reference to the Egyptian Guidelines for Medical Device Vigilance System), and communicates them with the Medical Device Safety Department (MDSD - EPVC).

Signature

Title

Glossary

CE: Conformity European

DOC: Declaration of conformity

EDA: Egyptian Drug Authority

EPVC: Egyptian Pharmaceutical Vigilance Centre

FSCA: Field Safety Corrective Actions

FSNs: Effective Field Safety Notices

GMP: Good Manufacturing Practice

HEPA Filter: High-efficiency Particulate Air Filter

HVAC System: Heating, Ventilating, and Air Conditioning System

ISO: International Organization for Standardization

MDSD: Medical Device Safety Department

MIRs: Manufacturer Incident Reports

MSDS: Material Safety Data Sheets

PMS: Post-Market Surveillance

PSRs: Periodic Summary Reports

RO: Reverse Osmosis

SMH: Summary of Marketing History

SOP: Standard Operating Procedure