Regulatory Guide for Licensing Requirements of Medical devices Factories, and In vitro diagnostic medical devices
Year 2025

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Introduction

This regulatory guide contains the licensing requirements for medical devices and In Vitro diagnostics factories, as approved by the Licensing requirements Committee in accordance with Law No. 15 of 2017 and Law No. 151 of 2019

Scope

This guide sets the minimum licensing requirements for medical devices and In Virto diagnostics factories, cGXP based on laws, ministerial decrees, and the latest international guidelines. The Egyptian Drug Authority grants the technical license for operation after conducting the necessary licensing inspections to ensure compliance with the licensing requirements at these factories

Abbreviations

cGMP: Current good manufacturing practice
GXP: Good practice quality guidelines and regulations in various fields

WHO: World Health Organization

UPS: Uninterrupted Power Supply

SOP: Standard operating procedures

ISO: International Organization for Standardization

HEPA filter: High-efficiency particulate air filter

LAF: Laminar air flow

HVAC: Heating, Ventilation and air conditioning

UV lamp: Ultraviolet lamp

IQ: Installation qualification

OQ: Operational qualification

IVDR: In vitro diagnostic regulation-

ASTM: American Association for Testing and Measurement

RO: Reverse osmosis

MSDS: Material safety data sheet

Definitions:

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- In vitro diagnostic medical device according to directive European EC98/79/.
In vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information: o concerning a physiological or pathological state, or o concerning a congenital abnormality, or o to determine the safety and compatibility with potential recipients, or o to monitor therapeutic measures. Specimen receptacles are in vitro diagnostic medical devices.
'Specimen receptacles are those devices, whether vacuum-type or not, specifically intended by their manufacturers for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination. Products for general laboratory use are not included in in vitro diagnostic medical devices unless, based on their characteristics, they are specifically intended by their manufacturer for use in in vitro diagnostic examinations.
3-Non-sterile medical devices manufacturing factories are those that produce non-sterile medical devices and do not require a classified cleanroom for production and packaging

unless otherwise specified in the manufacturing specifications.
4- ready to be sterilized medical devices manufacturing factories that are sterilized before use are those that produce non-sterile medical devices that are ready for sterilization before use (they are sterilized by the user
5- Sterile medical devices manufacturing factories: are factories that produce sterile medical devices.

Classification of medical devices manufacturing factories

(This is in accordance with the licensed products list, and each new product is evaluated separately)

1- Factories manufacturing on-sterile medical devices (e.g., oxygen masks, ventilator tubes, (medical devices, protective supplies/ non-sterile medical clothing)

2-Factories manufacturing non-sterile medical devices, but are sterilized before use (e.g., (medical plates and screws, medical clothing prepared for sterilization)

3- Factories manufacturing sterile medical devices (e.g., surgical joints, medical syringes, (infusion sets, surgical gloves, sterile medical clothes)

4- Factories manufacturing in vitro diagnostic medical devices.
5) Factories manufacturing prosthetic limbs, orthotics, and mobility aids (requirements for factories manufacturing prosthetics, orthotics, AND MOBILITY AID are applied)

5- Factories manufacturing medical devices in the form of pharmaceutical dosage forms such as drops, nasal sprays, gels, creams, powders, ampoules, vials, and pre-filled syringes. Good Manufacturing Practices (GMP) requirements issued by the World Health Organization are applied.

medical devices Factory Licensing Requirements.

General Site Requirements: -

1-The production area must have dedicated entrances and exits.

2-No factory will be approved within a multi-story industrial complex if any step takes places in any classified cleanroom.

3-A clear sign bearing the factory name must be displayed

4-The height between the factory floor and the lower surface of the ceiling must be at least 2.60 meters

5-The floor of the factory must be at or above street level, except where sufficient precautions are taken to prevent water seepage into the ground floor below street level, including the installation of a drainage network at a suitable distance to prevent contamination.

6-An uninterruptible power supply (UPS) is preferred for operations or steps requiring uninterrupted power supply.

7-A separate production area must be provided for medical devices if other industrial activity exists. (in the case of non-sterile medical devices.)

8- Compliance with occupational safety, health, and fire prevention requirements as per Decree No. 864 of 2018.

1-Requirements for Non-Sterile Medical Devices Manufacturing Factories

These are factories that produce non-sterile medical devices and do not require a classified clean area for production and packaging unless the manufacturing specifications stipulate otherwise

Technical Requirements for the Factory:

1-Separate toilets, if present, from gowning rooms, toilets which shall be located before the gowning rooms.
2- shoe rack (an open stand for street shoes and another for toilets, if present) shall be provided
3 ventilation sources in toilets (if present) shall be provided
4- air curtains and insect traps shall be provided at all factory entrances directly facing the street.
5- tight wire mesh shall be installed over any ventilation opening in the factory (non-corrosive)
6- street shoes shall be separated from shoes worn inside the factory.
7- workers' outer clothes shall be separated from factory gown.
8-A ventilation source is required

Note: For medical devices containing water, a water treatment station (compliant with requirements) must be provided. Example: Ultrasound gel is not sterile

Facility and Equipment:

Warehouses:
If there is one warehouse, its size should be determined according to the nature of the product, and it should be internally divided into zones separated by Interspacing or Physical distance.

Warehouses are divided into the following zones, according to the nature of the final product and production components"
Receiving area
Raw material storage area
Packaging material storage area

The rejection area for finished products must be sealed and well-secured.
The finished product storage area must be secure.
The storage area for any raw materials or products requiring special storage conditions must adhere to the following requirements:
-A covered area /Canopy to ensure that products or raw materials are not exposed to sunlight or any weather changes during loading and unloading.
-ventilation shall be adequate.
-Temperature and humidity gauges must be installed, and the temperature and humidity levels must be appropriate for the nature of the product.

The flooring must be sturdy, for example, but not limited to, helicopter

A rodent control system must be in place
All warehouse doors must be tightly sealed to prevent the entry of rodents or insects
A tight wire mesh must be installed on any ventilation openings, and the glass must be tinted to prevent direct sunlight from entering.
The storage area must not have a water source.
Storage must not be directly on the floor alongside with Pallets or stands that meet good storage and industrial safety requirements. Storage must be 60 cm below the ceiling and 20 cm away from the walls.
If there is a separate warehouse for finished products, all the requirements must be met

Workers' preparation area before entering production areas (according to the specifications to produce materials)
Unclassified area
At least factory clothes, a head covering, and shoe covers must be worn in this area.
If workers need to change clothes and shoes, there must be lockers to separate everyday clothes and shoes from factory clothes, and these lockers must be suitable for the number of workers.
Good ventilation must be provided
Hand sanitizer must be available
Walls and floors must be sturdy with smooth surfaces
Illustrated instructions must be provided for workers regarding procedures before entering the production area

Production area

Products are produced, assembled, and packaged within this area, and the following requirements must be adhered to:

Unclassified Area

The area is designated for production only

If water is used in the production process, its entry and exit routes to and from the machines must be enclosed.

A suitable ventilation source must be provided to achieve the required temperature and humidity levels according to the nature of the product.

Temperature and humidity gauges must be installed

In the case of anesthesia and respiratory equipment, indirect ventilation (well-ventilated) is required; fans are not permitted.
Floors must be sturdy, smooth, and clean, such as tiles or epoxy.
A designated area must be provided for storing molds when needed
Laboratories (Laboratories are divided according to the nature of the final product)
A. Physicochemical Laboratory
-The laboratory must be in a separate room, considering:
-The space must be suitable for the number of employees and the type and size of the activity
A suitable place must be available for storing chemicals, chemicals must be stored according to the storage requirements stated on the containers.
-Safety measures must be applied in the laboratory
-The laboratory must be equipped with the necessary medical equipment, and all equipment must be calibrated.
If the physicochemical analysis of the product is performed during the manufacturing process, a separate laboratory may be waived, and it can be considered part of the production area.
-Contracting with an external laboratory is permitted "outsourcing"
B. Microbiology Laboratory
Contracting with an external laboratory subject to the supervision of the Egyptian Drug

Authority is permitted if the factory needs to perform certain tests

2-Requirements for factories manufacturing ready to be sterilized medical devices, which are sterilized before use

These are factories manufacturing non-sterile medical devices that are ready for sterilization before use (sterilized by the user). Production is not required to take place in a classified clean room, but packaging must be done in a designated (classified clean room).

A-Requirements for factories manufacturing ready to be sterilized textile products

Technical requirements for the factory

1-Separate toilets, if present, from gowning rooms, with toilets located before the gowning rooms.

2-Provide a shoe rack (an open stand for street shoes and another for toilets, if present)
3-Provide a ventilation source in toilets (if present)
4-Install air curtains and insect traps at all factory entrances directly facing the street.
5- Install tight wire mesh over any ventilation opening in the factory (non-corrosive)
6-Separate street shoes from shoes worn inside the factory.
7-Separate workers' outer clothing from factory gown.
8-A ventilation source is required

Facilities and Utilities

Warehouses

If there is one warehouse, the warehouse area must be considered. Based on the nature of the product and the requirement that the warehouse be internally divided into zones separated by physical or Inter-spacing **distances**
it is divided into the following zones: According to the nature of the final product and its production components:
1-Receiving area
2-Raw materials storage area
3-Packaging materials storage area
4-Rejection area, which must be sealed and well- secured.
5-Finished product storage area
A storage area for any raw materials or products requiring special storage conditions, adhering to the following requirements: -
A covered area/ canopy to ensure that products or raw materials are not exposed to sunlight or any weather changes during loading and unloading.
ventilation shall be adequate

Temperature and humidity gauges must be installed, and the temperature and humidity levels must be appropriate for the nature of the product.

The flooring must be sturdy, for example, but not limited to, helicopter
A rodent control system must be in place
All warehouse doors must be tightly sealed to prevent the entry of rodents or insects
A tight wire mesh must be installed on any ventilation openings, and the glass must be tinted to prevent direct sunlight from entering.
The storage area must not have a water source.
Storage must not be directly on the floor alongside with Pallets or stands that meet good storage and industrial safety requirements. Storage must be 60 cm below the ceiling and 20 cm away from the walls.
<u>If there is a separate warehouse for finished products, all the requirements must be met</u>
<u>Production Areas:</u>
<u>Gown Control Area</u>
1-Unclassified area
2-Lockers for both clothing and shoes must be provided, suitable for the number of workers in the area, along with a step-over bench made of coated metal or stainless steel)

3-A designated gowning room(s) must be provided for workers

4-Workers must change shoes before entering the production area

5-Workers' outer clothing must be kept separate from the clothing specific to the area they are entering
6-A source of ventilation is required.
7-washing basins are not allowed, and hand sanitizer must be present (Disinfectant)
8-Walls and floors must be sturdy with smooth surfaces. (stout, smooth)
9-Ventilation must be good and indirect; fans should not be present. Lighting must be adequate and covered.10-SOP must be established outlining the procedures for workers entering the controlled
area

<u>The controlled area</u>
It is the area where fabric is cut and sewn, and the following requirements must be met:
The controlled area must be separate.
A designated area must be provided for cleaning and removing the outer packaging of raw

materials before they enter the controlled room.
This area must be equipped with a ventilation source and an exhaust fan.
Indirect ventilation (well-ventilated) is required; fans are not permitted
Temperature and humidity gauges must be installed inside the controlled room, meeting the temperature and humidity requirements specified in the product specifications and material safety data sheet.
Flooring must be strong, smooth, and clean (e.g., tiles or epoxy)
Indirect ventilation (Supply and Return Air Network) is required
When the product is moved from the controlled room to the clean room, the following must be met:
It must be placed inside two double bags and then secured to the clean area using a classified airlock or a dynamic pass box.
B-It must be stored in an intermediate warehouse compliant with the good storage practices.
(Secondary gowning area)
is the area where clothes are changed before entering the clean room.
-Clothes are changed, then stepping overstep- over bench, and then clean room gowns are worn
(Secondary gowning)
-(Doors must be interlocked)
The area must be classified as Class D/ISO 8.
-Cascading of pressure must be monitored by installing pressure differential gauges so that:
The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should typically lie in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintentional crossflows due to turbulence.
The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.
i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa

the grills shouldn’t be office type

There must be SOP established to explain the procedures for workers entering the clean room.

<u>Clean room</u>:

-The area where medical devices are packaged

-Cascading of pressure m

must be monitored by installing pressure differential gauges so that:

The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should typically lie in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintentional crossflows due to turbulence.

The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.

i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa

-Doors should open in the cleaner direction, in the direction of higher pressure "more positive".

-The flooring must be strong and smooth, for example, epoxy or vinyl.

The walls must be smooth, and the wall-floor junction must be curved.

Temperature and humidity must be controlled so that the temperature does not exceed 22C ° 2± 22 and the humidity 5± %65 (The temperature supports the minimum permissible bacterial growth unless otherwise technical requirements are specified.)

Pressure gauges must be installed at all doors, and dynamic pass boxes must be installed in the clean room.

Supply grilles must be present in the ceiling and return grilles must be present in the ceiling or side walls. If return grilles are present in the side walls, they must be at a suitable distance for air return.

Grills must not be of the office type.

The height between the floor and ceiling must be at least 2.60 meters.

The number of air change rate should be between 15-20 cycle /h.

according to ISO 14644

<u>HVAC system: (air handling unit)</u>

This unit includes:

-Prefilter

-Secondary filter (Bag filter)

-Heavy-efficiency particulate air (HEPA) filter

-Pressure gauges are located at the prefilter and bag filter, as well as before and after the high-quality HEPA filter

The air handling unit should be in a dedicated technical room or covered with a canopy. The floor should be tiled, and the surrounding area should be clean.
-The necessary tests must be conducted to ensure the safety of the air handling unit.

<u>Laboratories are classified according to the nature of the final product:</u>

A-Physicochemical Laboratory: The laboratory should be in a separate room, considering: The space should be suitable for the number of employees, the Nature and scale of the activity.
A suitable place should be available for storing chemicals, and storage should be carried out according to the storage requirements stated on the containers.
Safety measures should be applied in the laboratory.
The laboratory should be equipped with the necessary instruments according to medical requirements, and all instruments should be calibrated.
If the physicochemical analysis of the product is performed during the manufacturing process, a separate laboratory may be required, and it can be considered part of the production process
Contracting with an external laboratory is permitted

<u>B- Microbiological Laboratory</u>: The laboratory should be a controlled area. It must have a separate entrance divided internally into areas isolated from each other by interspaces or physical separation." to prevent. cross contamination
According to the following laboratory activities:
Washing area
Preparation area
(Incubators area (the number of incubators must not be less than 2).
Autoclave for sterilization.
Autoclave for destruction.
area containing a unit Laminar airflow.
All equipment must be calibrated.
Differential pressure measuring devices must be present.
Temperature and humidity measuring devices must be present in the laboratory.
-If water is used, type and source of the water used should be specified.

-If contracting with an external laboratory that meets the requirements, the contracted laboratory must be subject to oversight by the Egyptian Drug Authority for the tests to be conducted there (environmental control tests for the clean area and microbiological tests performed on the product). The laboratory must also provide the SOPS (Specific Sample Collection and Transportation) procedures for sampling and transformations (Handling and transformation) . If the factory violates this condition during operation, measures will be taken in accordance with the regulations and decisions governing this matter, pursuant to Laws 15 of 2017 and 151 of 2019

"Sterilization: "Performed by the user

Valid & Approved method of sterilization

The sterilization method approved by the factory must be included in the packaging

B. Requirements for Factories manufacturing Orthopedic Surgical Supplies and Instruments

Technical Factory Requirements:

1-Separate toilets, if present, from gowning rooms, with toilets located before the gowning rooms.

2-Provide a shoe rack (an open stand for street shoes and another for toilets, if present)

3-Provide a ventilation source in toilets (if present)

4-Install air curtains and insect traps at all factory entrances directly facing the street.

5- Install tight wire mesh over any ventilation opening in the factory (non-corrosive)

6-Separate street shoes from shoes worn inside the factory.

7-Separate workers' outer clothing from factory gown.

8-A ventilation source is required

Facilities and Equipment:

Warehouses:

If there is one warehouse, its size should be determined according to the nature of the product, and it should be internally divided into zones separated by Interspacing or Physical distance.

Warehouses are divided into the following zones, according to the nature of the final product and production components"

Receiving area

Raw material storage area

Packaging material storage area

-The rejection area for finished products must be sealed and well-secured.

The finished product storage area.
The storage area for any raw materials or products requiring special storage conditions.
<u>and must adhere to the following requirements:</u>
-A covered area/canpy to ensure that products or raw materials are not exposed to sunlight or any weather changes during loading and unloading from and to the stores.
- ventilation shall be adequate
Temperature and humidity gauges must be installed, and the temperature and humidity
Floor Systems must be sturdy, for example, but not limited to, helicopter.
A rodent control system must be in place.
All warehouse doors must be tightly sealed to prevent the entry of rodents or insects.
A tight wire mesh must be installed on any ventilation openings, and the glass must be tinted to prevent direct sunlight from entering.
The storage area must not have a water source.
Storage must not be directly on the floor alongside with Pallets or stands that meet good storage and industrial safety requirements. Storage must be 60 cm below the ceiling and 20 cm away from the walls.
<u>If there is a separate warehouse for finished products, all the requirements must be met</u>

<u>Workers' preparation area before entering production areas</u> (according to the specifications of the production of the item)
-Unclassified area
-At least factory clothes, a head covering, and shoe covers must be worn in this area.
-If workers need to change clothes and shoes, there must be lockers to separate everyday clothes and shoes from factory clothes, and these lockers must be suitable for the number of workers.
-Good ventilation must be provided
-Hand sanitizer must be available. (disinfectant)
-Walls and floors must be sturdy with smooth surfaces.
-Illustrated instructions must be provided for workers regarding procedures before entering the production area.

<u>Production Area</u>
-Products are manufactured within this area, which must adhere to the following requirements
-Unclassified area
-The area must be separate
-If water is used in the production process, the water inlet and outlet to and from the

machinery must be enclosed.
-Availability of a suitable ventilation source to achieve the required temperature and humidity levels.
-Availability of appropriate temperature and humidity measurements according to threshold limits and safety procedures, while meeting the specific temperature and humidity requirements as per the product specifications and material safety data sheet.
-Floors must be sturdy, smooth, and clean.
-A designated area must be provided for storing molds when needed
Polishing Area: (Separate area)
-Availability of an indirect (well-ventilated) ventilation source. Fans are not permitted
-Walls and floors must be sturdy with smooth, clean, and soft surfaces.
-The drain in sinks used for washing must be sanitary
-Availability of temperature and humidity gauges, meeting the specific temperature and humidity requirements as per the product specifications and material safety data sheet.
Laser Marking Stage: The stage where data is printed on the product
1-Availability of an indirect (well-ventilated) ventilation source with fans not permitted.
2-Walls and floors must be sturdy with smooth, clean surfaces
3-Temperature and humidity gauges must be present, meeting the specific temperature and humidity requirements according to the product specifications and safety data sheet.
4-water source is not promoted
Washing area (Controlled area)

"It is the area where medical devices are washed and dried before entering the clean area"

1-A separate, not air classified area

2-Air used to dry products must be oil & water free

3-The drain in the wash basins must be a sanitary sink

4-Indirect ventilation (well-ventilated) must be present (fans not permitted)

5-Temperature and humidity gauges must be present, meeting the temperature and humidity requirements according to the product specification and material safety data sheet.

6-Floors must be sturdy, smooth, and clean

7-Return & supply grills must be available

8-If the product is moving from the controlled room to the clean room, the following must be met:
A-It must be placed inside a double bag and then passed to the clean area via a classified airlock or a dynamic pass box.
B-to be stored in an intermediate storage area that meets good storage requirements.
<u>(Secondary gowning area)</u>
is the area where clothes are changed before entering the clean room.
-Clothes are changed, then stepping over step- over bench, and then clean room gown are worn
(Secondary gowning)
-(Doors must be interlocked)
The area must be classified as Class D/ISO 8.
-Cascading of pressure must be monitored by installing pressure differential gauges so that:
The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should typically lie in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintentional crossflows due to turbulence.
The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.
i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa
the grills shouldn't be office type.
A Standard Operating Procedure (SOP) explaining the procedures for workers entering the cleanroom should be in place.

<u>Clean Room</u>:

-The area where the final product is packaged.
-Pressure cascading is maintained by installing pressure differential gauges so that
The pressure differential between adjacent cleanrooms of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.
i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa

-Doors should open in the cleaner direction, in the direction of higher pressure "more positive".
-The flooring must be strong and smooth, for example, epoxy or vinyl.
-The walls must be smooth, and the wall-floor junction must be curved.
-Temperature and humidity must be controlled so that the temperature does not exceed 22C ° 2± 22 and the humidity 5± %65 (The temperature supports the minimum permissible bacterial growth unless otherwise technical requirements are specified.)
-Pressure gauges must be installed at all doors, and dynamic pass boxes must be installed in the clean room.
-Supply grilles must be present in the ceiling and return grilles must be present in the ceiling or side walls. If return grilles are present in the side walls, they must be at a suitable distance for air return.
-Grills must not be of the office type.
-The height between the floor and ceiling must be at least 2.60 meters.
-The number of air change rate should be between 15-20 cycle /h.
according to ISO 14644

<u>HVAC system: (air handling unit)</u>

This unit includes:
-Prefilter
-Secondary filter (Bag filter)
-Heavy-efficiency particulate air (HEPA) filter
-Pressure gauges are located at the prefilter and bag filter, as well as before and after the high-quality HEPA filter
-The air handling unit should be in a dedicated technical room or covered with a canopy. The floor should be tiled, and the surrounding area should be clean.
-The necessary tests must be conducted to ensure the safety of the air handling unit.

<u>Water Treatment Station</u>

A water treatment station is established if the nature of the product requires the use of treated water, provided that the station complies with the requirements

If the water is supplied from an external source (a factory subject to the supervision of the Egyptian Drug Authority), the contract concluded with the supplier and water analysis certificates must be submitted.

(Laboratories: Laboratories are divided according to the nature of the final product)
A. Physicochemical Laboratory:
The laboratory is in a separate room, taking into consideration:
-The space must be suitable for the number of employees and the type and size of the activity.
-A suitable place must be available for storing chemicals, and chemicals must be stored according to the storage requirements stated on the containers
-Safety measures must be applied in the laboratory
-The laboratory must be equipped with the necessary equipment according to medical requirements, and all equipment must be calibrated
. If the physicochemical analysis of the product is performed during the manufacturing process, a separate laboratory may be required, and it can be considered part of the production process

-Contracting with an external laboratory is permitted "outsourcing"
B. Microbiological Laboratory: The laboratory must be a controlled area with a separate entrance divided internally into areas isolated from each other by Physical separation or interspaces to prevent cross-contamination, according to the following laboratory activities:
Washing area
Preparation area
Incubators area (with a minimum of two incubators)
(Autoclave for sterilization area)
(((Autoclave for destruction area)
(Laminar air flow (LAF) area
All equipment must be calibrated.

- Pressure gauges must be present.
- Temperature and humidity measuring devices must be present in the laboratory
-If water is used, the type and source of the water used should be specified

If contracting with an external laboratory that meets the aforementioned requirements, - the contracted laboratory must be subject to oversight by the Egyptian Drug Authority for the tests to be conducted there (environmental control tests for the clean area and microbiological tests performed on the product). The laboratory must also provide the SOPS (Specific Sample Collection and Transportation) procedures for sampling and

transformations (Handling and transformation) . If the factory violates this condition during operation, measures will be taken in accordance with the regulations and decisions governing this matter, pursuant to Laws 15 of 2017 and 151 of 2019

Sterilization: performed by User

The manufacturer's approved sterilization method is included inside the packaging
Valid & Approved method of sterilization

Requirements for factories manufacturing sterile medical devices
such as surgical joints, syringes, IV Administration Set, surgical gloves, and sterile medical gowns.

Technical Requirements for the Factory:
1-Separate toilets, if present, from gowning rooms, with toilets located before the gowning rooms.

2-Provide a shoe rack (an open stand for street shoes and another for toilets, if present)

3-Provide a ventilation source in toilets (if present)

4-Install air curtains and insect traps at all factory entrances directly facing the street.

5- Install tight wire mesh over any ventilation opening in the factory (non-corrosive)

6-Safety measures for workers within the factory must be applied

7- A generator is required for operations or processes that require uninterrupted power supply.
Factory Gowning Area

This is the area where streetwear is replaced with factory wear. It is unclassified and the following must be observed:
-Street shoes must be kept separate from shoes worn inside the factory
-Workers' outer clothing must be kept separate from factory gown
-A source of ventilation is required
- An exhaust fan shall be installed

Warehouses

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 material storage area
-Sampling area (classified as the production area if powders are used as raw materials) or
-Inspection area (under controlled environmental conditions)
-Weighing area (if powders are used as raw materials) classified as Class D/ISO 8
-Rejection area for the final product (must be secured and sealed)
-Finished product storage area
-A storage area for any raw materials or products requiring special storage conditions

The following requirements must be observed in warehouses:

-If there is only one warehouse, its size must be appropriate for the nature of the product and it must be internally divided into separate areas, either by physical or spatial spacing.
●A covered area /canopy is required to ensure that products or raw materials are not exposed to sunlight or any weather changes during loading from and to the stores.
-A receiving area with the following requirements:
-Double doors with an electronic interlock system
-Equipped with an air curtain and insect traps

-Ventilation must be the same as the rest of the warehouse
-Good ventilation must be ensured
-Temperature and humidity measuring devices must be installed.
-Temperature and humidity levels must be maintained at the appropriate levels according to the nature of the product
-Flooring must be sturdy, for example, helicopter
-A rodent control system must be in place.
-All warehouse doors must be tightly sealed to prevent the entry of dust or insects.
-Tight wire mesh must be installed on any ventilation openings, and the glass must be screened to prevent direct sunlight from entering

-Lighting shall be adequate
-There must be no direct water source in the storage area.

-Storage must not be directly on the floor alongside with Pallets or stands that meet good storage and industrial safety requirements. Storage must be 60 cm below the ceiling and 20 cm away from the walls
-If there is a separate warehouse for finished products, all the above requirements must be met

Gown control area:
Unclassified area
Lockers for both clothing and shoes must be provided number of lockers shall be suitable for the number of workers in the area, along with a step-over bench (made of coated metal or stainless steel)

-There Shall be Designate separate gowning rooms for women and men
- The shoes should be replaced with ones specifically designed for the area.

- workers' outer clothing Shall be Separated from the clothing required for the area being entered
- adequate ventilation shall be ensured
-washing basins are not allowed, and hand sanitizer/disinfectant must be available
-Walls and floors must be sturdy with smooth surfaces and no visible joints, stout, smooth
-Good, indirect and adequate ventilation (no fans) shall be available, as well as good and covered lighting
Controlled Room
This is the area where raw materials or intermediate products are produced, provided that these materials do not support bacterial growth.
The following requirements must be met
-The area is Unclassified
-The controlled area must be separate (not used as a passageway)
-If water is used in the production process, its entry and exit routes to and from the machines must be enclosed.
-A designated area must be provided for cleaning and removing the outer packaging of raw materials before they enter the controlled room. This area must be equipped with a ventilation source and an exhaust fan.
-Indirect ventilation (well-ventilated) is required; fans are not permitted
-Temperature and humidity measuring devices must be installed inside the controlled room, meeting the specific temperature and humidity requirements as per the product specifications and material safety data sheet.

-The flooring must be strong, smooth, and clean (e.g., but not limited to, tiles or epoxy.
-A designated area must be provided for storing molds, attached to the controlled room, as needed.
-If the product is moved from the controlled room to the clean room, the following must be met:
A-It must be placed inside two double bags and then passed to the clean area via a classified airlock or a dynamic pass box
B-It must be stored in an intermediate storage area that meets good storage requirements.

(Secondary gowning area).

- is the area where clothes are changed before entering the clean room.
-Clothes are changed, then stepping over a step- over bench, and then clean room gown is worn
-(Doors must be interlocked)
The area must be classified as Class D/ISO 8 According to the product's manufacturing specifications, Cascading of pressure must be ensured if manufacturing takes place within a classified area above Class D/ISO 8.
-Cascading of pressure must be monitored by installing pressure differential gauges so that:
The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should typically lie in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintentional crossflows due to turbulence.
i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa
the grills shouldn't be office type.

Clean Room:
-The clean room is the area where production, assembly, printing, and packaging take place.
-It must be an air-classified according to the manufacturing specifications for the materials, with a minimum rating of Class D/ISO.
-It must be preceded by a secondary gowning area where the following occurs: changing clothes, then passing over a step bench, and finally putting on cleanroom clothes (secondary gowning)

The doors shall be interlocked (synchronized doors)
-The changing room that precedes the cleanroom must have the same air classification as the cleanroom.
-Pressure cascading is maintained by installing pressure differential gauges so that The pressure differential between adjacent cleanrooms of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.
i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa
-Doors should open in the cleaner direction, in the direction of higher pressure "more positive".

-The flooring must be sturdy and smooth, for example, epoxy or vinyl.-
-The walls must be smooth, and the wall-floor junction must be curved.
-Temperature and humidity must be controlled so that the temperature does not exceed 22C ° 2± 22 and the humidity 5± %65 (The temperature supports the minimum permissible bacterial growth unless otherwise technical requirements are specified.)

-for printing on the product, the printing must take place inside the cleanroom, and if inks are used, the ink application area must be physically separated.
-If printing is done outside the cleanroom, justification must be provided.
-Raw materials must enter through (aerated/dynamic pass box) or a (classified airlock))
- pressure differential gauges shall be installed at Dynamic pass boxes in cleanrooms) -)
-Supply grilles must be present in the ceiling and return grilles must be present in the ceiling or side walls. If return grilles are present in the side walls, they must be at a suitable distance for air return.
-Grills must not be of the office type .
-The height between the floor and ceiling must be at least 2.60 meters.
-The number of air change rate should be between 15-20 cycle /h.
according to ISO 14644.

<u>HVAC system: (air handling unit)</u>
This unit includes:
-Prefilter
-Secondary filter (Bag filter)
-Heavy-efficiency particulate air (HEPA) filter

-Pressure gauges are located at the prefilter and bag filter, as well as before and after the high-quality HEPA filter

-The air handling unit should be in a dedicated technical room or covered with a canopy. The floor should be tiled, and the surrounding area should be clean.
-The necessary tests must be conducted to ensure the safety of the air handling unit.

(Water Treatment Station)

"A water treatment plant is established if water a is used in the manufacture of a medical device
The water treatment station consists of the following parts:
a. City water tank (made from stainless steel grade 316 L, or polyethylene, or polypropylene)
b. Sand filter
c. Carbon filter (activated granular carbon), at least one filter
d. 2 (duplex) softeners
e. Storage tank for soft water
f. Reverse osmosis or ion exchange resin or electrodialysis (for water purification)
g- UV lamp
h. bacterial filter 0.2 micron
i. Stainless steel tank for storage of purified water (Storage conditions are either above ◦85 C or below ◦25 C.
The following requirements must be observed at the water treatment station
-The water specifications shall meet the specifications of the medical device
-All rust-causing metals (iron, aluminum, copper) must be excluded.
-A spray ball or air filter should be used inside the purified water tank.
-There should be a spray ball and vent filter in the purified water storage tank.
-Dead legs (ends) must be avoided to prevent contamination.
-There should be continuous water circulation (no stagnancy)
-Daily monitoring of water at multiple sampling points is necessary.
-All water storage tanks should be identified, and water flow directions should be labeled.

If water is outsourced (a factory shall be subject to the Egyptian Drug Authority's oversight), the contract with the supplier and water analysis certificates must be submitted.

Laboratories are classified according to the nature of the final product:

A-Physicochemical Laboratory:

The laboratory should be in a separate area, taking into account:

-The space should be suitable for the number of employees, the Nature and scale of the activity.

-A suitable place should be available for storing chemicals, and storage should be carried out according to the storage requirements stated on the containers.

-Safety measures should be applied in the laboratory.

-The laboratory should be equipped with the necessary instruments according to medical requirements, and all instruments should be calibrated.

-If the physicochemical analysis of the product is performed during the manufacturing process, a separate laboratory may not be required, and it can be considered part of the production process.

-Contracting with an external laboratory is permitted.

B- Microbiological Laboratory:

The laboratory should be a controlled area.

-It must have a separate entrance divided internally into areas isolated from each other by interspaces and physical separations. "Cross contamination" According to the following laboratory activities:

1-Washing area

2-Preparation area

3-(Incubators area (the number of incubators must not be less than 2).

4-Autoclave for sterilization area.

5-Autoclave for destruction area.

6- Laminar airflow area (LAF)

Its specifications are as follows:

The surrounding area must have the same air classification as the production room, with a minimum classification of ISO 8/Class D.

It must be preceded by an airlock for changing clothes (gowning), classified as Class D/ISO 8

-The floor must be covered with a smooth, jointless material with technical specifications no less than epoxy. The wall-floor junction must be curved.

-A dynamic pass box must be present in the LAF room.

- All equipment must be calibrated.

-Differential pressure measuring devices must be present

-Temperature and humidity measuring devices must be present in the laboratory

-If water is used, the type and source of the water must be specified

-If contracting with an external laboratory that meets the requirements, the contracted laboratory must be subject to oversight by the Egyptian Drug Authority for the tests to be conducted there (environmental control tests for the clean area and microbiological tests performed on the product). The laboratory must also provide the SOPS (Specific Sample Collection and Transportation) procedures for sampling and transformation (Handling and transformation). If the factory violates this condition during operation, measures will be taken in accordance with the regulations and decisions governing this matter, pursuant to Laws 15 of 2017 and 151 of 2019

Sterilization:

If sterilization methods other than mentioned are used, each case will be reviewed individually.

A. In the case of sterilization using gamma radiation,

the medical devices Factories Inspection Department verifies the existence of a contract between the factory and the Atomic Energy Authority.

B. In the case of steam sterilization:

- the availability of an approved calibration certificate is required.

-The validation study is monitored by the medical devices Factories Inspection Department.

-If a water treatment factory is used, the specific requirements for the water treatment factory must be followed.

-If the factory does not have a water treatment station, a water softener is used at the water inlet of the pressure furnace (autoclave) used for sterilization.

(In the case of gas sterilization (e.g.: ethylene oxide / nitrogen dioxide)

manufacturer's acceptance certificates shall be present: (Acceptance test, operational qualification, and Installation qualification)

-Sterilization should be carried out in a separate area with exhaust fans.

-Provide a secure storage area for gas cylinders (with empty and full cylinders kept separate).

-Use appropriate pallets according to the manufacturer's operating instructions.

Regarding the ventilation room

A-The room area must be suitable for the size of the sterilizer (the area must be sufficient for the maximum number of sterilization cycles during the 48-hour incubation period of the biological indicator.

B. Temperature and humidity measuring devices must be present

C. heaters must be provided if needed.

-If the factory allocates an area for pre-conditioning, a thermal mapping of this area must be provided.
-A ventilation area is unnecessary if the sterilization unit is proven capable of performing sufficient washing to reach the limits of residual ethylene oxide.
The storage area must be large enough to hold batches for 48 hours until the results of the microbiological tests for the biological indicator are available.

Contracting with an external factory to perform the sterilization process is permitted, provided that: -
-The external factory is subject to inspection by the Egyptian Drug Authority's Pharmaceutical Inspection Department.
- If the factory contracts with another factory not subject to inspection by the Egyptian Drug Authority, it must provide a written undertaking confirming its willingness to allow pharmaceutical inspectors to access to the factory, which is responsible for sterilization, at any time.

Note: If the factory does not comply with any of the above requirements due to the nature of manufacturing medical devices, it must submit studies supported by a report and reference confirming this and present them to the committee responsible for factory licensing.

Production areas for In vitro diagnostic medical devices manufacturing factories are classified according to the microbiological status of the product, the risk assessment study submitted by the industrial facility (which is its responsibility), and the manufacturing specifications (if any)

General Site Requirements:

1-The production area must have dedicated entrances and exits.

2-No factory will be approved within a multi-story industrial complex if any takes places in any classified cleanroom.

3-A clear sign bearing the factory name must be displayed

4-The height between the factory floor and the lower surface of the ceiling must be at least 2.60 meters

5-The floor of the factory must be at or above street level, except where sufficient precautions are taken to prevent water seepage into the ground floor below street level, including the installation of a drainage network at a suitable distance to prevent contamination.

6-A generator connected to the factory's electrical circuit must be provided if there are special requirements related to manufacturing or storing the product.

7-The equipment and machinery that operate on main electricity and generators must be clearly identified in an engineering drawing, which should be provided upon request.

8-It is preferable to provide an uninterrupted power supply (UPS) for operations or steps that require a continuous power supply.

Worker Entrance Area

1- toilets shall be separated from changing rooms, ensuring toilets are located before the changing area

2- shoe racks (an open stand for street shoes and another for factory shoes) shall be provided

3- ventilation shall be provided in toilets

4- air curtains and insect traps shall be installed at all factory entrances facing the street

Changing Area

Is the area where street clothes are changed into factory clothes, which is an unclassified Aeration Area.
1-Separate street shoes from shoes worn inside the factory
2- workers' outdoor clothes shall be separated from factory clothing
3- ventilation with an exhaust fan shall be installed
4- Lockers - Step over bench should be made of coated metal or stainless steel.

5- Designate a changing area(s) for workers shall be provided
6- dedicate locker for outdoor clothing and another for factory clothing shall be provided
7- No water source in the changing area is allowed.
8- disinfectant for hand sanitization (Disinfectant) shall be provided
9- Walls and floors must be strong with smooth surfaces. If there are joints (multiple joints), they must be treated according to industry standards to prevent the accumulation of any dust or particles and to be as smooth as the floors.
10-Ventilation must be adequate
11- Lighting must be adequate and covered
12- Fine, rust-resistant tight wire mesh must be placed over any ventilation opening to protect against flying insects or pests.

Warehouses

Areas are divided into the following
according to the nature of the final product and production inputs:
Raw material storage area
Packaging material storage area
Reject area for the final product, which must be tightly sealed and secured
Finished product storage area
Area for any raw materials or products requiring special storage conditions,
and the following requirements must be adhered to:
1-Warehouses must be well-ventilated
2-There must be a covered area with a canopy to ensure that products or raw materials are not exposed to sunlight or any weather changes During loading and unloading to and from the warehouses.
3-Storage requirements for products/raw materials must be met
4-Temperature and humidity measuring devices must be present.
5-Floors must be sturdy
6-Rodent control measures must be followed
7-All warehouse doors must be tightly sealed to prevent the entry of dust and insects
8-A fine wire mesh must be placed over all ventilation openings, and the glass must be tinted to prevent direct sunlight from entering.
9-Adequate lighting must be provided

10-A water source is not allowed in the storage area
11-Direct storage on the ground is not allowed. Pallets/stands must be provided, conforming to good storage and industrial safety requirements. Storage must be 60 cm below the ceiling and 20 cm away from the walls.
12- If a refrigerator is required, the following must be met:
A-It must be equipped with calibrated thermometers

B-Temperature must be monitored and recorded periodically.
Water systems (Water station)
If water is used in manufacturing, the factory must have a water station that meets the necessary requirements for water production, in accordance with the technical specifications stipulated in the product's technical specifications or the specifications for laboratory water use stipulated in the latest editions of ASTM (American Association for Testing and Measurement)
In the case of outsourcing of water, the factory must meet the requirements stipulated in the section of Material control.
-The water station may consist of Miniature devices made of RO unit without pre-treatment, in case of small quantities (100 liters per day). If the factory requires more than this amount, a complete water treatment station must be provided, including:
1-Sand filter
2-Micron Filter
3-water softener
4-Carbon filter or sodium metabisulphite injection system
5-RO unit, followed by another RO stage if required by specifications
-If using water directly without storage, small RO devices or a water treatment station can be used, depending on production needs.
-If water is used in quantities requiring storage during production processes, this storage must be through a closed loop, with both inlet and outlet through this closed loop.
-The factory must conduct and document water tests to ensure compliance with requirements
Labs
1-Specific requirements for each product regarding analysis must be met. For example, if products require microbiology analysis, a microbiology laboratory with all the necessary equipment to conduct the required tests is essential.
2- If the factory does not have a quality control or microbiology laboratory, it is obligated to contract with a licensed external

laboratory. This laboratory will be inspected to ensure it meets all the necessary requirements for conducting tests on the factory's products related to their evaluation and analysis.
3-The contract must include a clause allowing for laboratory inspections regarding the analysis of the contracted products. The laboratory is obligated to provide the records
4-All necessary equipment for conducting tests must be available according to the product requirements.
5-All equipment used in the laboratory must meet the standard calibration requirements in the laboratory.
6- Labeling must be provided to indicate the calibration status of the equipment, its calibration validity, and the date of recalibration

Material control

1-A list of approved suppliers must be available.
2-A supplier selection checklist must be maintained
3-The selection criteria must include quality, safety, and performance standards.

Controlled room:

This is the area where products are manufactured and packaged that do not require production in cleanroom
1-It must be separate and not used as a passageway
2-A suitable ventilation source must be provided
3-Preferably, the temperature should not exceed 2± 22 C and the humidity 5± 65 % unless there are specific technical requirements for the product.
4-If the IVD produced require a lower humidity level, a dehumidifier or another engineering method must be provided to achieve the required humidity.
5-The specific requirements for each product regarding temperature and humidity must be met according to the product data and specifications certificate or the Material Safety Data Sheet (MSDS)
6-Temperature and humidity gauges and any other gauges attached to equipment or production machinery whose accuracy affects the safety of the desired product must be calibrated
7-The floor must be smooth, clean, and sturdy
8- A designated area must be attached to the controlled room for storing reagents when needed.
9- The production stage must be separate from the packaging stage

Secondary gowning area:

-This is the area where clothes are changed before entering the clean room.

1-There must be SOP established to explain the procedures for workers entering the clean room.

2- Clothes are changed, then stepping over a step- over bench, and then clean room gown is worn

Doors must be interlocked3-

4-The area must be classified as Class D/ISO 8 According to the product's manufacturing specifications, Cascading of pressure must be ensured if manufacturing takes place within a classified area above Class D/ISO 8.

5- Cascading of pressure must be monitored by installing pressure differential gauges so that:

The pressure differential between adjacent cleanrooms or clean zones of different cleanliness levels should typically lie in the range of 5 Pa to 20 Pa, to allow doors to be opened and to avoid unintentional crossflows due to turbulence.

i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa

the grills shouldn't be office type.

Clean Room:

- The clean room is the area where products that require production in a air classified - clean room are produced and packaged.

-It must be preceded by a changing/gowning area with the same classification as the cleanroom.

-Calibrated Pressure differential gauges must be installed between rooms

-Pressure cascading is maintained by installing pressure differential gauges so that

The pressure differential between adjacent cleanrooms of different cleanliness levels should be between 5 Pa to 20 Pa, which allows doors to be opened and prevents unintentional crossflows due to turbulence.

i.e., Between rooms of different grades should have a pressure differential of approximately (10-15) ±5Pa

-Doors should open in the cleaner direction, in the direction of higher pressure "more positive".

-Floors and walls should be smooth, and the junction between walls on one side and the ceiling or floors on the other should be rounded or semi-circular (curved)

-Calibrated gauges should be installed to measure temperature and humidity.

-the temperature should not exceed 2± 22° C and the humidity 5± 65 % unless there are specific technical requirements for the product.

-If printing is done on the product, it must be done in a clean room. If using inks, physical separation must be installed.

-Materials should be introduced through a dynamic pass box/classified air lock
-A supply grill and a return grill must be present in the ceiling or side walls. If a return grill is present in the side walls, it should be at a suitable distance for air return.
-The height between the ceiling and floors must not be less than 2.6 meters.

-The air change rate must conform to the class, for example
Class D: Number of air changes from 15 to 20 changes per hour according to ISO standard 14644
-The production stage must be separate from the filling/packaging stage.

<u>HVAC System Air Handling Unit</u>

-The Air Handling Unit must include the following: Pre-filter/Bag Filter/HEPA filter
-A pressure gauge must be installed at the pre-filter and bag filter, as well as a pressure gauge before and after the HEPA filter.
-The air handling unit must be covered with a canopy, the floor must be tiled, and the surrounding area must be clean.
-The necessary tests must be conducted to ensure the safety of the air handling unit and its compliance with the requirements.

Note:
If the factory does not apply any of the above requirements due to the nature of manufacturing invitro diagnostic, the factory must submit studies supported by justification and reference that confirm this and present them to the committee responsible for licensing the factory.

References

-Law No. 15 of 2017
-Law No. 151 of 2019
-Requirements for Factories of Prosthetics, Orthotics, and Mobility Aids
-ISO 14644:2015: Cleanrooms and associated controlled environments
-ISO 11135:2014: Sterilization of health-care products Ethylene oxide - Requirements for the development, validation and routine control of a sterilization process for medical devices.
-ISO 13485:2016: Medical devices - Quality management systems - Requirements for regulatory purposes

-ISO 17025:2017: General requirements for the competence of testing and calibration laboratories
-ISO 11607: Packaging for terminally sterilized medical devices
-IVDR: EU-In Vitro Diagnostic Regulation
-MDR: EU-Medical devices regulation