

PRODUCTS

DRUG DELIVERY

CONTRACT DEVELOPMENT

PHARMACEUTICAL
INNOVATORS

FACTSHEET

Clinical Manufacturing





OctoPlus' facilities enable the production of final dosage forms for:

- + parenteral solutions (aseptically prepared or sterilized via autoclaving)
- + lyophilized products
- + special products such as liposomes and microspheres
- + creams and ointments

The parenteral zone is equipped with:

- + double-door vial washer
- + double-door steam sterilizer
- + double-door dry heat oven
- + filling machine with special precision pump for small volumes (1 ml up to 50 ml)
- + filling pump for manual filling
- + steam sterilisable lyophilizer (2.5 m² plate capacity) with automatic stoppering device
- + capping machine
- + equipment for the preparation of complex formulations (e.g. homogeniser)

OctoPlus' clinical manufacturing facilities

OctoPlus has been operating a small-scale clinical manufacturing plant in Leiden, the Netherlands since 2000. The facilities consist of three floors: the ground floor is dedicated to small-scale GMP production of parenteral dosage forms, and warehousing, respectively. Formulation of parenterals, as well as filling and finishing is done in a dedicated section of the ground floor with separate entrance and air handling. The first floor is dedicated to laboratories for stability testing and analytical activities such as development and release testing. The second floor comprises offices and utilities.

Classified areas

The classification of the production areas in the plant is as follows: the aseptic filling room is a Grade A (laminar air flow) in Grade B environment (European GMP) or a Class 100 in 10.000 room (Federal Standard 209E). Both machine and manual fills are possible. With respect to machine filling, the laminar air flow area covers the filling machine from the stopper bowl and vial inlet through to lyophilizer loading. Manual filling takes place in a LAF cabinet. The filling point is monitored continuously for non-viable particle counts during operation.

The filling machine or LAF cabinet and the surrounding grade B environment are monitored before, during and after filling for viable air and/or surface counts. The adjacent areas such as the vial preparation room and formulation room are all classified as Grade C or Class 100.000. The production areas are entered via a gowning room into a transport "neutral" zone (controlled but not classified).

Clinical manufacturing

General

Incoming goods are stored in special areas for Quarantine, Released and Rejected status. A cold room is available for storage of temperature-sensitive products. Entrance into the warehouse and production areas is restricted to authorized personnel. Sampling and weighing of the raw material is performed in a dedicated sampling area and a central weighing suite, respectively. The route for final products is separated from the incoming goods; storage of final products is done in designated areas in the warehouse while they are awaiting shipment.

Several clothing and cleaning procedures in the controlled transport zone and production area ensure full quality compliance. In addition, a technical area is located in between the production zone and the area for formulation development. Here, the water for injection equipment is located, as well as the technical installation of the lyophilizer.

Parenteral production

The parenteral production suites include an aseptic filling room (grade A in B), preparation and washing rooms (grade C) and a formulation suite (grade C). Gowning rooms are placed to enter the classified C and B suites, respectively. It is possible to store products under quarantine in special freezers or refrigerators (-20 °C and 2-8 °C, respectively) in a dedicated room.

The parenteral formulation area is equipped with state-of-the-art equipment for pharmaceutical operations. For development purposes, a research lyophilizer and various testing facilities such as differential scanning calorimetry equipment are available outside the production area.

Non-parenteral production

OctoPlus has the expertise to develop and manufacture a wide variety of dosage forms for non-parenteral applications, such as capsules, ointments and creams. OctoPlus has established a network of partners for the manufacturing of clinical trial material for non-parenteral dosage forms, a network that can be put to use whenever necessary, but with OctoPlus remaining responsible for project coordination and release and stability studies. OctoPlus' expertise in this area and the established network provides our partners with the possibility to move non-parenteral formulations rapidly from pharmaceutical development to manufacturing of clinical trial material.

Coding, labeling and packaging

Coding and labeling is performed in the neutral zone. Packaging for shipment is performed in a dedicated area in the warehouse.

Analytical laboratories

General

The analytical laboratories are used for method development, method validation, analytical support and quality control. The analytical laboratories are located on the first floor and are organized per discipline:

Analytical chemistry

Available methods are a.o. : HPLC, IR and UV spectrometry, titrimetry, coulometric analysis, dissolution testing, differential scanning calorimetry, thermogravimetric analysis and osmolarity and other pharmacopoeial methods.

Analytical biochemistry

The following methods and others are available: HPLC (size exclusion chromatography, reversed phase chromatography, ionexchange chromatography, affinity chromatography), SDSPAGE (Sodium dodecyl Sulphate Polyacrylamide Gel Electrophoresis), IEF (Iso-electric focusing), UV spectrometry, turbidimetry and LC-MS-MS.

Immunochemistry

Immunochemistry involves quantification and identification of proteins and peptides in in-process controls and final product, using techniques such as ELISA (Enzyme Linked Immunosorbent Assay), and quality control using tissue culture techniques and bioassays. Other techniques involve a.o. endotoxin testing. Other analytical techniques are available on request.

Building utilities

HVAC system

The facility is supplied with different Heating, Ventilation, Air Conditioning or HVAC systems for parenteral manufacturing, formulation development and the laboratories, respectively. The pressure settings are continuously monitored by a building monitoring system, as applicable for the temperatures and relative humidity of classified areas and stability cabinets. In the pilot plant the supply air is filtered locally through ceiling-mounted HEPA filters. In the aseptic filling room the air is supplied via plenums with HEPA filters. The air change rate is 140 times per hour, whereby the air is partly re-circulated. The pressure in the filling room is maintained at over-pressure.

Water and steam

Potable water is de-chlorinated through an active charcoal filter, 5 µm filtered and used as feed for a De-Ionisation (DI) System plus supply of raw water to the building. Incoming water is monitored for bioburden and absence of coliforms by routine sampling and testing.

The De-Ionised Water System (DI) consists of cation/ anion exchange units, periodically regenerated and used alternately. The DI water is used to supply the house steam installation via a break tank. Furthermore, passing several filters, two distribution loops for the laboratories are fed from this system. The quality of the DI loop is controlled via the routine water-monitoring program. The loops are sanitized by heat shock on a regular basis.

A Water for Injection system (WFI) is installed in a separate technical area on the ground floor. The WFI system consists of a quadruple distiller, which is fed with purified water from a Reversed Osmosis device. The WFI distribution system consists of a holding tank and piping systems in loops with local heat exchangers. The WFI is circulated at 85 °C through the entire system. If needed, part of the WFI can be cooled via local heat exchangers.

The WFI distribution system is continuously monitored and controlled with respect to temperature and conductivity, and the system automatically discards the water before re-entering the holding tank should one or both limits be exceeded. The quality of the WFI is monitored by regular sampling and complies with the European and U.S.P. monograph for Water for Injections. WFI is used in glassware washers, the formulation area and vials and stopper preparation.

Compressed air/gasses

Oil- and particle free, dry pressurized air is generated by a compressor supplying a storage vessel. Process air/ clean air and instrument air is distributed to the application points. Industrial gasses such as nitrogen are supplied through distribution networks. All gasses are supplied from bottles and released by our Quality Assurance department according to the applicable specification regarding identity and purity.

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