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AZ Fachverlage AG

Detail of filling line. The motors and moving parts of the automatic filling machine are oil free.

BIOPROCESSING

Tailored Cell Culture Media – Produced in a Cleanroom of GMP Standard

Production of sterile high quality media of big batch sizes requires a lot of technology. BioConcept, manufacturer of the Amimed tissue culture media, invested in a new cleanroom of pharmaceutical standard and a water purification system in order to produce Water for Injection, liquid and powder cell culture media of the highest quality available for customers. A GMP certification is in process.

When working in a biological laboratory with cell cultures, one gets in touch with cell culture media, powdery ones, to prepare with water, or liquid ones, ready to use. Manufacturer of such media in Switzerland is BioConcept. The company was founded in 1978 and has therefore almost 40 years of experience in serving the Swiss biological community with labware – since 1993 also with an own brand of tissue culture products and media, the Amimed product line. BioConcept has become a leading supplier and service partner for numerous reputable pharmaceutical and academic institutions in Switzerland.

The purpose with Amimed was to manufacture tissue culture products for the sophisticated and evolving pharmaceutical and bio-pharmaceutical markets. With its product range, BioConcept has developed a strong international presence. Nevertheless, the company is still situated in Basel in Switzerland. In Allschwil, a broad range of special and standard media are manufactured in order to create the ideal cell growth medium and other sterile liquids tailored to meet the customer's needs.

Liquid II goes GMP Cleanroom

August 2015 represents a further milestone in BioConcept's history: In the course of development and progress, the enterprise designed and built a new production line called Liquid II, which is a liquid media plant. Liquid II is currently approaching its completion and will be inaugurated. The new automated liquid handling processing line meets pharmaceutical GMP standards. It is made of stainless steel, is situated in a GMP class A (or ISO class 5) cleanroom and has a batch capacity of up to 5000 l/day. There are many requirements to

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meet, when building a cleanroom. Therefore, intensive planning is necessary as well as exact implementation and validating.

The new plant was designed to create a surrounding that ensures a high degree of sterility, ensuring a sterile final product. A state of the art air processing system is used to supply the optimal conditions needed for sterile liquid production. The air-conditioning is a very important factor in the process of manufacturing pharmaceutical substances. Pressure, temperature, humidity and particle count in the air are constantly monitored and controlled in order to maintain air quality of GMP class A / ISO class 5 standards. The monitoring improves consistency of the procedures or detects early possible deviations that may arise.

A regular H_2O_2 disinfection ensures sterility of the cleanrooms. The Hydrogen Peroxide Vapour (HPV) equipment basing on spinning disk technology is used to produce a fine fog of uniform and controlled droplets of 5–10 µm size. The machine disinfects the designated space effectively without using nozzles or compressed air.

The rooms and facility have been integrated in the original building. 1000 m^2 of new production and storage space offers the operators to work in an environment equipped with the latest technolo-

01 Glimpse at the clean room and its airlock. The cleanroom is designed to enable a smooth workflow of product and personnel.

02 The automatic filling line can fill up to 2000 500 ml bottles of media in one hour. For the preparation of the bottles a cleanroom robot is used, which assures a high standard

03 The filling machine is located in the centre of the plant and made almost entirely of stainless steel.

Interview

5 Questions from Life Sciences plus addressed to Martin Howald, CEO of BioConcept

LS+ (Sonja Bichsel): Mr. Howald, what was the motivation for BioConcept to invest a lot of money and build the high standard production line Liquid II?

Martin Howald: We had to react to the increase in inquiries we were receiving from the cell culture market. Our existing production plant, Liquid I, only has manual filling, so we were unable to fulfil all inquiries. So the logical consequence was to increase and automate our production capabilities.

LS+: Who are the typical customers ordering BioConcept's media?

Martin Howald: Our typical customers work in research as well as biopharmaceutical and pharmaceutical production worldwide. Customers of products produced by Liquid II will not differ from our current customer base, but as we are specialized in customized products, we are open for all other inquiries beside the usual customer applications.

LS+: A project like Liquid II is time consuming, how long did it take to realize it?

Martin Howald: It took us one year from the start of planning to the final completion. All the planning was executed in-house, we did not work with external architects or engineering companies.

LS+: What are the major challenges when building a new production line?

Martin Howald: The major challenge was the short time frame of 1 year and – concerning the given building structure – the implementation of Liquid II without disturbing our running production.

LS+: What significance does a GMP certification have for the biotechnological and life science industry?

Martin Howald: GMP plays a key role for our customers working in biopharma and pharmaceutical production. As a supplier for these customers we need to have a GMP certificate in order to be accepted as a trustworthy supplier. We started already in 2005 in our ISO 9001 certificate with working according to GMP standards. For the new Liquid II plant we will achieve a GMP certificate.

gies and materials. The working place is spacious and easy to access, thus the plant can be run conveniently and the products are rapidly transferred to the appropriate storage due to the close proximity of the new storage rooms. A large proportion of the interior has been made from well-sized windows. A lot of glass has been used in order to make the plant more open and transparent. This layout is arranged to make it possible to inspect one side of the plant whilst standing on the other. The transparency concept allows the staff to easily overlook the whole production process, which in turn is monitored by state of the art sensors and visualised on several user interfaces, integrated into the plant's structures.

The company's offices are also in close vicinity, on the floor above. With the location, the interior and automation of the processes, BioConcept has increased managing and monitoring of the manufacturing process, in order to produce quick but with highest quality possible.

For custom made products, delivery time is about six weeks upon order. These products can include customer designed media (powder or liquid), individual solutions for cell cultures, cell system applications, buffers and balanced salt solutions or supplements and auxiliary reagents. The products are then manufactured in accordance to the customer's recipe. Sterilisation can be done by filtration with 2 µm filters or by vapour sterilization. Customers can also choose the container for the product filling: a variety of size and types including glass, sterile bags or PET bottles of different volumes. Batch sizes range from 5 to 5000 l or 2 to 800 kg, respectively.

Water and Vapour

Chemically and microbiologically pure water is a key component in manufacturing liquid biopharmaceutical medium. Therefore, BioConcept invested into a new water purification facility. The system is engineered to efficiently generate Water for Injection (WFI), water of the highest approved pharmacopoeia standard. The facility now produces up to 5000 l of media per day, which meets the rising demands of the customers.

The process to transform regular tap water to WFI usually starts with reverse osmosis. Quality of the resulting highly purified water has to be monitored constantly. Therefore, pH and osmolarity as well as conductivity, endotoxin and bioburden levels have to be determined and recorded.

The purified water is either integrated in the cleaning system of the facility or is turned into pure steam by a powerful electric steam generator.

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The three new media filling stations can handle up to three 500 liter containers simultaneously.

For production of WFI, the pure steam is condensed. During this process the heat is extracted and recycled into the air conditioning system. It is then used to control the humidity and temperature of the rooms. WFI has to be kept at a constant temperature above 80 °C to avoid microbiological contamination. To maintain a sustainable and constant temperature, the energy from the heat exchangers is recycled around the water circuits. This is monitored constantly using sensors. Besides WFI production, the generated steam has other purposes within the manufacturing process: it is connected to the Clean-in-Place / Sterilize-in-Place (CIP/SIP) systems and the sterilizer.

The use of an electric steam generator instead of the commonly used petrol powered alternative reduces carbon emissions of the company. The loops of purified water and steam for cleaning and heating purposes save electricity and therefore contribute to the plant being more ecological and financially sustainable.

Automated Production

A high quality vapour sterilizer is designed to disinfect solid and porous products such as filters, rubber stoppers, and system components. The sterile filters are customarily disinfected in order to avoid cross-contamination. Integrity tests monitor each of the filters to make sure they are operating correctly. This represents a reliable GMP-compliant design.

In their new facility, BioConcept uses state of the art machinery such as an automatic filling system as well as three media filling stations that are designed to fill large containers. The modern sensors and equipment are used to assure a high level of accuracy and flexibility when measuring product parameters. Its capacity ranges from 100 l/day to 5000 l/day and has the possibility to handle various bottle and container types from 100 ml to 500 l.

The automatic filling line can fill up to 2000 500 ml bottles of media in one hour. For the preparation of the bottles, a cleanroom robot is used, which assures a high standard. All further steps, such as sealing and labelling, are also performed automatically. The motors and moving parts of the automatic filling machine are oil free, which reduces the risk of contamination.

The three new media filling stations can handle up to three 500 liter containers simultaneously. This allows completing even big batch sizes within one day. The media pipes and tanks are made out of pharmaceutical standard electropolished stainless steel and are linked to the CIP/SIP system.

BioConcept is proud of their new state of the art liquid media plant called Liquid II. The plant has been designed to maximize efficiency, sustainability and productivity through utilizing modern technology and focusing on the fine detail of the plants design. The design of the new plant and the equipment used are currently in accordance with GMP guidelines and the company is in the process of being certified.

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