DENSITY GRADIENT MEDIA

Production of Axis-Shield Density Gradient Media

Axis-Shield Density Gradient Media are produced by Fresenius Kabi Norway AS, a subsidiary of Fresenius AG.

With its comprehensive range of products in combination with responsive services Fresenius Kabi has a unique position in its business fields and is the European leader in infusion and nutrition therapy.

Dedication to quality is an integral part of the culture and values at Fresenius Kabi. They provide thorough evaluation and testing of all manufactured materials in modern, fully equipped, quality-control laboratories. Their facilities operate under strict FDA and EU cGMP compliance. The use of highly automated production equipment combined with experienced personnel who have a total commitment to cGMP, further ensure product quality and customer satisfaction.

The production operations follow the routines prescribed in the production documentation, where all steps in the process are defined.

Cleaning

The mixing tanks, the pipelines and the filling equipment are cleaned with Water for Injection. All cleaning procedures are thoroughly tested and validated to ensure clean tanks between manufacturing of different products. In order to conserve the microbiological integrity of the product, the entire production line is treated with water for injection ≥ 80°C at regular intervals.

Preparation of the solution

The production takes place in grade C areas. Mixing is performed in large stainless steel tanks. The mixing tank, which is placed on weight cells is filled with Water for Injection. Active ingredients and the required excipients are added and the mixture is agitated until completely dissolved. After a fixed stirring time, samples are taken for physical, chemical and microbiological in-process analyses. When the product has achieved the required physical and chemical specifications, the product is ready for filtration and filling.

Preparation of the bottle

The bottle is made of pharmaceutical grade polypropylene. The bottles are moulded according to an injection blow moulding principle following four steps:

- Heating of the granulate to approx. 220°C to form the parison and to perform the treads and bottle body.
- Conditioning and adjustment of temperature
- Blow moulding: The parison is stretched lengthwise by a stretch pin and blown to its final shape.
- Ejection of finished bottles from the machine onto the conveyor belt.

Web:

www.axis-shield-density-gradient-media.com

AXIS-SHIELD

PO Box 6863 Rodelokka
N-0504 Oslo
Norway
Phone: +47 24 05 60 00
Fax: +47 24 05 60 10
Email: bjh@no.axis-shield.com or
john@jgrescon.fsbusiness.co.uk

Filling

The transport of the bottles from the moulding machine, filling and capping of bottles are carried out under conditions given in PIC regulations grade A.

The solution is filtrated through a membrane filter before filling. The pre-cleaned filling line, filter and filling machine are flushed with solution prior to filling.

The bottles are filled to a volume not less than nominal volume. The filling is performed according to a mass flow meter principle. The bottles are capped immediately after filling. After filling and capping, the bottles are stacked in autoclave racks and are ready for sterilization.

At specified intervals samples are withdrawn in order to verify correct filling volumes and functional testing. Samples for bio burden and endotoxin testing are collected during the process. A filter integrity test is performed before and after filling.

Sterilization

The filled bottles are subjected to a validated steam sterilization cycle on the day of mixing and filling. The autoclave is computer controlled and operates by means of clean steam, distilled water and compressed air. It gives a sterilization cycle at 121°C which ensures that a minimum of F_0 value =12 is delivered to the product.

Packaging

The filled sterilized units are visually inspected, labelled and packed into transport cartons.

Container/Closure information

The material of the bottles is a copolymer of polypropylene and ethylene. The bottleneck is especially designed to support the excellent and controlled pouring qualities and the octagonal shaped body of the bottle supports a firm grip. The bottles are supplied with a screw cap. The design of the screw cap ensures that the bottle can be reopened several times. It has a pilfer-proof ring, which is broken when the bottle is opened for the first time. The screw cap consists of a white polypropylene shell and a polypropylene plug or a perfusable cap with white shell with an aluminium pealable lid and a chlorobutyl rubber stopper that seals the bottle. The perfusable screw cap is designed to be used as an ordinary screw cap or allow for a spike to be inserted through the top of the cap and further down through the rubber plug. The top of the cap is covered with a protective aluminium lid, which is pealed off before use. The caps are pre-assembled by the manufacturer.

Quality control/Quality assurance

After production the products are controlled in the QC laboratory for pH, density and osmolality. The specification on density is within ± 0.001 g/ml of the desired value. The specification on osmolality is within ± 15 mOsm of the desired value. The content of endotoxin should be less than 1.0 EU/ml (according to European Pharmaceutical Standards). However, our goal is to produce batches with endotoxin content less than 0.13 EU/ml.

The Fresenius Kabi quality system meets the requirements of the NS-EN ISO 9001.

AXIS-SHIELD
Innovation for Life