Description of the manufacturing process

The product is manufactured in compliance with the standards cGMP.

The dedicated area to the product manufacturing is classified in accordance to the standard EN ISO 14644/GMP. The bulk preparation is carried out in class A areas; the automatic refill of the syringes is carried out within a class A LAF (laminar air flow) in a class C room.
The clean rooms, where the product is manufactured, are periodically re-evaluated (HVAC SYSTEM).

The productive process is briefly described below.

The process starts with the preparation of a Hyaluronic Acid solution obtained by fermentation through *Streptococcus Equi* (with a pH 2.7-3.0 in order to ease the solubilisation), a small quantity of buffer solution is added to that and after that also cross-linked agent (BDDE, butanediol diglycidyl ether) at 50°C.

The solution is cooled up to room temperature; HCI is added to it to stop the solution and obtain the forming of 32 “blocks”. These are maintained in a cold closed container for two days.

A solution of non-reticular Hyaluronic Acid (together with a certain quantity of buffer solution) is prepared on the fourth dal and is added to the previous solution. 5 litres of solution are therefore obtained and are Kept, for an extra two days in a buffer solution in order to facilitate the dialysis process (cleaning and leakage of the residual BDDE). A further process of homogenisation is then carried out.

Controls in-process

The last day, the seventh one, the filling of syringes starts together with the steam sterilization in autoclave.

The sterilization process is carried out in accordance to harmonized regulations EN 554 ed ISO 17665.

The relative registration to the sterilization process used during each process are kept for 5 years after the lot expiry date to which it refers to. The relative data necessary for the sterilization process validation are kept for 10 years.

Checks in-process

For what concerns buffer solution pH and osmolarity are checked.

The following checks are carried out:

- at the beginning (preparation of the starting solution)
- during the dialysis
- once the 5 litres of solution are obtained

Once the syringes are filled, they are checked for viscosity and volume.

During the dialysis process different part of the room are checked in order to be sure the dialysis will proceed correctly in all its parts following the accepted parameters; the *swelling rate* is also evaluated.

Checks on the finished products

Analysis are carried out on the finished product, all reported in the analysis Certificate (CoA).

The product packaging is carried out in accordance with one's SOPs; during the packaging phase quality checks on all packaging and wrapping materials are carried out. They will be discarded in case of non-compliance to internal guide lines.