ADAPTATION OF HOSPITAL ASEPTIC PROCESSES TO FACE NATIONAL SHORTAGE OF CURARE

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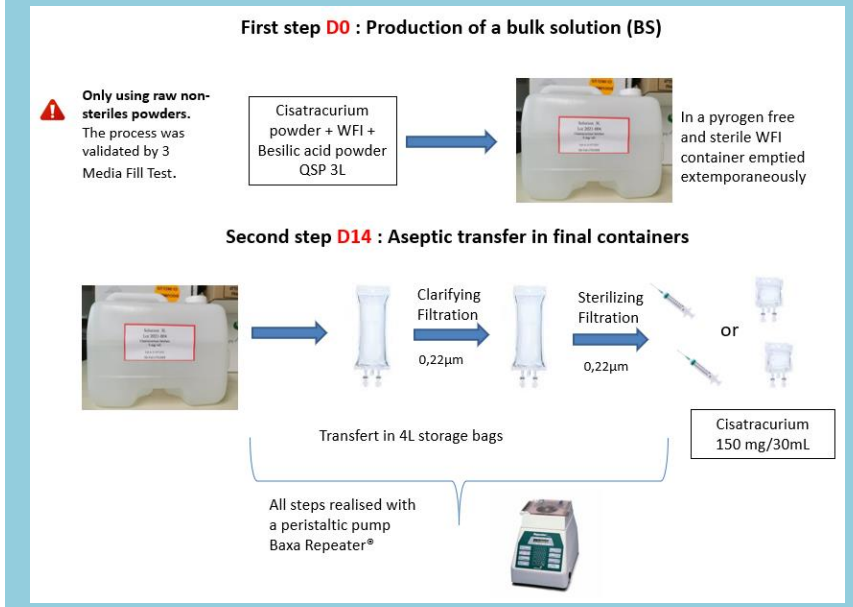
Introduction : In the context of essential drug shortages during the Covid-19 pandemic crisis, our team was involved in the network driven by ANSM for studying feasibility of hospital pharmacy production of curare and particularly in cisatracurium. The objective of this work was to validate the possibility to produce final ready-to-use curare solution, using current hospital aseptic methods and final containers i.e. bags and syringes. Benefits expected would be to improve the national capacity in case of major industry shortage.

MATÉRIALS AND MÉTHODS



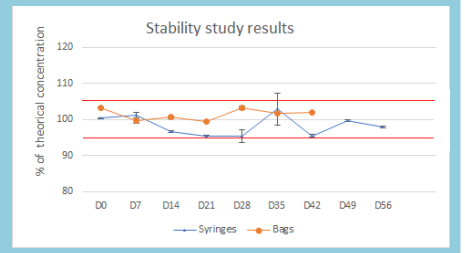
Third step :
- **Release controls on finished products** Cf. results table.
- **Process controls** : Filter integrity test (USP) and control of bioburden before filtration
- **Stability study using an HPLC (*) stability indicating method**: On BS at D0 and D14 and on finished products until D54

(*)Adapted from the method of Pignard et al. Stationary phase = Nucléoshell® RP18, 4µm, 150*4.6 mm; Mobile phase = 60% aqueous phase, 20% acetonitrile, 20% methanol. Detection at 280nm by diode array spectrophotometer

RESULTS

Test	Target value	Results
pH (n=3)	3 -3,7	3,51 ± 0,02 for syringes 3,62 ± 0,5 for bag
Osmolarity (n=3)	10-30 mOsm/kg	13 ± 2 for syringes 14 ± 0 for bags
Endotoxin (n=3)	<54.74 EU/mL	<15,0 EU/mL for both
Sterility (n=10)	No growth	No growth for both
Non-visible particles (n=10)	< 6000 per container for particles ≥ 10µm	175 ± 156 for syringes 978 ± 778 for bags
	< 600 per container for particles ≥ 25µm	8 ± 15 for syringes 8 ± 8 for bags
Visible particles (n=100)	No particle	No particle on syringes batch. One white particle on bags batch.
Extractible volume (n=1)	≥30 mL	31 mL for the syringe 30 mL for the bag
Leak test (n=5) (USP)	No coloration	No coloration for both

- All release controls were compliant with the European Pharmacopea (Ph. Eur) or USP
- No microbiological growth detected for the bioburden → the bacterial load before filtration was already null.
- All filters used during production had integrity.
- Cisatracurium concentration in BS and syringes were within +/- 5% along the study.
  → Expiracy date was set-up at 2 months after syringes production stored at +4°C.
- Stability study on bags is in progress.



Conclusion : Our method avoids the cost and delay associated with the use of more specialized equipment and allows the production of Ph. Eur. compliant products. Syringes can be stored two month at 4°C and bags for at least a month according to first results. The stability of our BS opens the possibility of subcontracting its repartition to other centers that have less technical and/or human resources.