

Implementation of Dose Banding of Nivolumab

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Introduction :

During our search for molecules that can be produced in dose banded chemotherapy, Nivolumab appeared to be an excellent candidate, its **fixed** dose of 240 mg covering almost all of our production; and allowing an easy management.

These infusions can be produced in 2 different isolators: manually in both or with a pump in one.

Materials and methods :

- 1) Verification of the stability of the diluted Nivolumab solution.
- 2) Process qualification by carrying out 3 Media Fill Test (MFT) for each manufacturing condition
MFT = Test simulating the manufacturing of a chemotherapy infusion by replacing the solvent and active molecule with culture medium.
 - **Beforehand:** Fertility test of MFT batches: seeding of 2 separate bags of MFT by *C. albicans* and *S. aureus* and culture for 14 days.
 - **Then:** Manufacturing of 9 MFT, involving all the operators.
=> Putting in oven (32,5°C ± 2,5°C) and checking of the bags at D3, D7 (turning of bags), D10 and D14.



Material for MFT manufacturing

- 3) Validation of the manufacturing process and storage methods by a **sterility test**: injection of water for injection into a solvent bag, and microbiological analysis at D21.
- 4) Definition of our optimal stocks and addition of the dose banded of Nivolumab in Chimio®.
- 5) Comparison of the average dispensing time of Nivolumab infusions before and after the implementation of dose banding.

Results :

- 1) The diluted solution of Nivolumab is stable for 28 days. [1]
- 2) Fertility tests were compliant after 14 days of culture.
No turbidity were observed in any of the MFTs.
- 3) No microbiological contamination was found during sterility tests.
- 4) The allocation of dose banded of Nivolumab is easily managed by the "Dose Banding" tool of Chimio®.
- 5) Average dispensing time :
Before: 25 minutes [6 minutes - 83 minutes].
After: **6 minutes** [1 minute - 14 minutes].



Fertility



MFT without turbidity



Sterility

Conclusion :

Our activity has been smoothed, allowing us to reduce the dispensing time of the Nivolumab infusions and therefore the waiting time of the patients. Our unit is already manufacturing 5 other dose banded molecules and is currently looking for new candidates to further improve our performance.



Turbidity-free MFT bag after 14 days in the oven

[1] Vieillard V, Bardo P, Akrouit W, Le Guyader G, Astier A, Paul M. Stabilité physico-chimique de solutions diluées de Nivolumab à 1 mois, 2017.