French 2019 Good Manufacturing Practice : larger batchs

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Context

French Good Manufacturing Practice (GMP) published in public inquiry in July 2019 would give the **possibility to produce up to 7 500 capsules per batch** versus 300 previously. In anticipation of the implementation of this new GPP, we have considered a **new manufacturing process** **to optimize batch management** by increasing from 300 to 1,500 capsules per batch. The objective of this work is to assess the feasibility of such a process at the scale of a hospital pharmacy by comparing it to the process used until now.

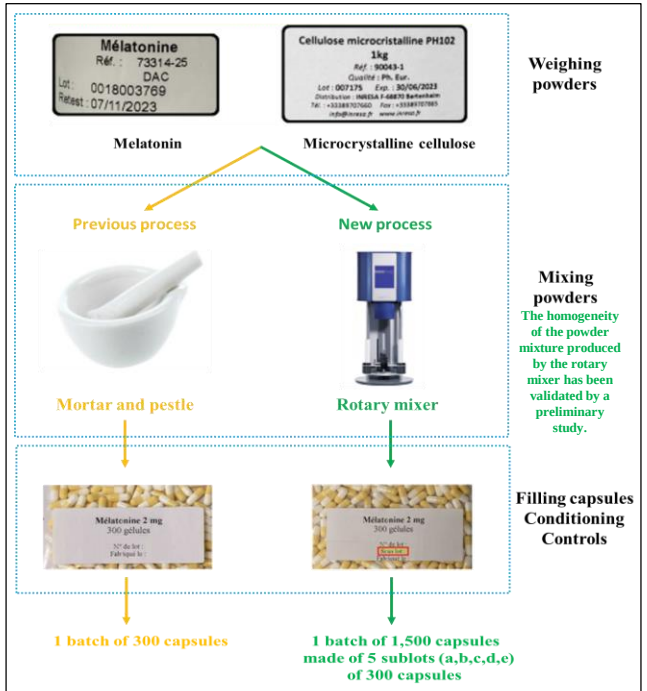
Material and method

To carry out this work, several elements were used:
- 2019 edition of GMP (*).
- R® software to perform statistical tests and graphical représentations.
- Microsoft Excel® software for the design of tables.
- COPILOTE® software to extract the consumption data of melatonin capsules on a one-year period.

(*) : https://www.ansm.sante.fr/content/download/163971/2143491/version/3/file/BPP_Enquete-Publique_Juillet-2019.pdf

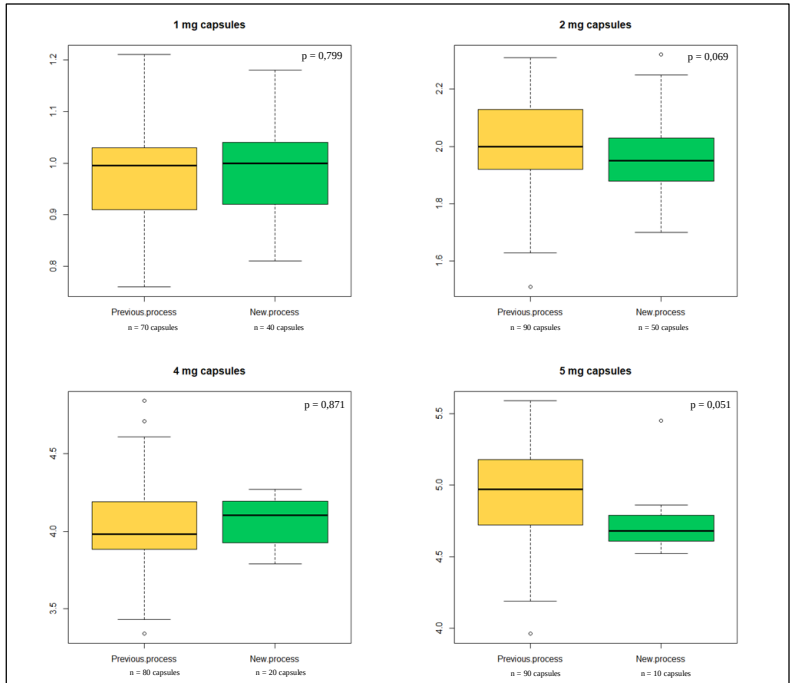
Results

Update of the manufacturing process



⇒ The **new process** include a **tolerance of 5% in the quantities** of powders **to be used**.

Comparison of the two processes : capsule content



⇒ **No significant difference** ($\alpha = 0.05$) between the two process in term of mean melatonin content.

Comparison of the two processes : time and yield

	Steps	Previous process (300 capsules/Batch)	New process (1,500 capsules/Batch)
Estimated time	Weighing powders	5 min	8 min
	Mixing powders	5 min	15 min
	Filling capsules	15 min	80 min
	Conditioning	15 min	23 min
	Controls	100 min	110 min
	Total	**2.3 hours per batch**	**3.9 hours per batch**
		0.467 min per capsule	0.157 min per capsule
Yield	Capsules → content uniformity test	10 up to 30 capsules	10 up to 30 capsules
	Capsules → sample library	20 capsules	20 capsules
	Maximum yield	**270 capsules per batch**	**1470 capsules per batch**
		90%	**98%**

Uniformity tests :
1) 20 capsules were used to perform the mass uniformity test according to the European Pharmacopoeia (2.9.5 - 9th edition) and reintroduced into each sublot (new process) or each batch (previous process). Compliant sublots were combined to form a single batch.

2) 10 up to 30 capsules were used to perform the uniformity of content test according to the European Pharmacopoeia (2.9.6 - 9th edition) for each batch.

Consumption analysis

Melatonin content	Capsules dispensed for hospitalized patients	Number of lots in circulation
1 mg	2216	15
1.5 mg	257	3
2 mg	4436	25
4 mg	2507	14
5 mg	742	8
Total	**10158**	**65**

Consumption on a one-year period, from 04/30/2019 to 04/30/2020

It do not include capsules delivered to other hospitals.

Discussion

The new process seems to be realisable at the scale of a hospital pharmacy. This one simplified the weighing step of the powders by allowing a maximal difference of 5% in the quantities of powders to be used. Increase the number of unit per batch would reduce the number of circulating batchs and so improve the gestion of the product. Moreover, increasing the size of the batches saves time over all the steps with an equivalent number of capsules produced. Thereby, producing 1,500 capsules would be almost 3 times faster with the new process. However, a non-conformity in a 1,500 capsules batch results in a greater loss. In order to **assess this compromise**, it might be interesting to **compare the number of non-compliant batches between the new and the previous process**. These tests have enabled us to think about optimizing the production, control, packaging and management of melatonin batches.