To
Ms. Shuang Zhao
Assistant Editor
Pharmaceuticals

Manuscript ID: pharmaceuticals-624980
Manuscript title: “Thermosensitive nanosystems associated with hyperthermia for cancer treatment: a systematic review”.

Dear editor

The manuscript was revised according to the reviewers’ comments. The authors would like to express their gratitude for their time to review the manuscript, and for their contributions, which much improved the final version of the manuscript. Please find enclosed the revised manuscript containing the changes (highlighted in yellow). Below, please find a point-by-point response to the reviewer’s comments.

- **Reviewer 4**
The review submitted by Pereira Gomes et al. to Pharmaceuticals describes various thermosensitive systems proposed for cancer treatment.
1) The great lack of this work is the almost total absence of references in the text. This makes it really difficult for a reviewer to judge the novelty and the accuracy of the work, even if references are reported at the end of the work.

  - **Answer:** There was an error submitting the article and all the references have been deleted. Therefore, we put all references back in their due place.

2) The use of English should be accurately checked as there are many mistakes and non-sense sentences in the text that prevent fluid reading:
lines 228-230
lines 401-402, lines 449-450

  - **Answer:** the manuscript was completely revised by a native speaker (Dr. Danyelle Townsend – co-author of this manuscript).
lines 462-463: same sentence repeated in a few lines, review this paragraph.

- **Answer:** This paragraph has been rewritten.

Thermos-sensitive: this expression, used many times by the authors, does not exist. It should be thermo-sensitive, thermo-sensitive or thermo-responsive.

- **Answer:** All 'thermos-sensitive' have been replaced by thermosensitive.

lines 530-532
and many others, please check the use of english.

- **Answer:** the manuscript was completely revised by a native speaker (Dr. Danyelle Townsend – co-author of this manuscript).

Moreover, in order to improve the quality of the manuscript:

3) Table 1. Please add references and indicate the years in which clinical trials took place.
Line 185-187: please add reference
Line 195-196: add reference

- **Answer:** There was an error submitting the article and all the references have been deleted. Therefore, we put all references back in their due place.

4) describe with more details the HIFU technique (which intensity? why focused? how it works? is it applicable to all tissues and body regions?).

- **Answer:** This information has been added to the chapter 3, with more details the HIFU technique (lines 205-241).

Line 218-223: add references

- **Answer:** There was an error submitting the article and all the references have been deleted. Therefore, we put all references back in their due place.
5) add a paragraph about thermosensitive hydrogels in part 4.

- **Answer:** The " 4.1.2 " section has been expanded by adding more information and examples of hydrogels.

6) as polymeric micelles are assembled into this form only above CMC, please discuss their stability after in vivo injection.

**Answer:** As suggested by the reviewer a sentence was added to the main text in order to discuss in vivo stability of self-assembled particles (lines 397-400).

7) Figure 2. define Tc (Critical Temperature): it could be not clear to non-expert readers, so it should be defined at least one time in the text or in the caption.

- **Answer:** The phase transition temperature is described in the text. In order to ensure understanding, a complete definition has been added to the text (lines 521-524).

8) please briefly describe the mechanism of action of radio-frequency ablation. how is it obtained? How the setup was applied to patients?

- **Answer:** A paragraph was added to the section “3” (lines 229-241) as suggested by the reviewer.