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 2**

  The paper “Thermosensitive nanosystems associated with hyperthermia for cancer treatment: a systematic review” is a review on thermosensitive system associated with moderate hyperthermia. It is an interesting subject, however there are many flaws in the manuscript that need to be changed for publication in Pharmaceuticals.

  In the introduction (paragraph 1), the objective of the review is the description of the thermosensitive nanosystems used in preclinical and clinical studies associated with moderate hyperthermia. It is an interesting subject, however there are many flaws in the manuscript that need to be changed for publication in Pharmaceuticals.

  In the final part of paragraph 4, the objective of the revision becomes the description of the most common nanocarriers used for a thermo-responsive antitumor drug release. Perhaps it is necessary to correctly focus the objectives of this revision.

  - **Answer:** We have changed paragraph 1 (lines 35-37 and lines 57-60) to give consistency with aim proposed in the paragraph 4.

It should be noted that other revisions related to thermosensitive nanosystems have been found in the literature and it is suggested to add among the references, such as Sanchez-Moreno P. et
- **Answer:** As suggested by the reviewer, the reference Sanchéz-Moreno 2018 (ref #7) was included in topic 1 and topic 2 (lines 57 and 139). The reference Shao 2011 (Ref #3) was included in topic 1 and in topic 4 (lines 50 and 316). The reference Lopes 2018 (ref #4) was included in topic 1 and in topic 4 (lines 50 and 319).

I would suggest to center and expand the description paragraphs of the thermosensitive nanosystems for moderate hyperthermia.

- **Answer:** The section " 4 " has been expanded, adding more information and examples of polymeric nanocarrier and hydrogels.

The writing of the article needs revisions, for example "Cancer gástrico" in table 2.

- **Answer:** Sorry for this mistake the term was correct to “gastric cancer”. In addition, the manuscript was completely revised by a native speaker (Dr. Danyelle Townsend – co-author of this manuscript).

Line 143: Please, add DOX abbreviation for doxorubicin. Line159: The MRI abbreviation is being used without definition and introduced later in the manuscript (line 510). Line 182: MRI is an abbreviation for “Magnetic Resonance Imaging”, not “Magnetic Resonance”.

- **Answer:** Abbreviations have been changed.

Line 318: If the main objective is the one indicated at the end of paragraph 4 (see comment 1), please provide more details and references about "different drugs".

- **Answer:** The objective was corrected as suggested in comment 1. Moreover, additional information/references were included (lines 387-390).
Through 4.1.2: The paragraph is too short and doesn't provide exhaustive information about the core-shell nanoparticles. Please expand and include examples and references.

- **Answer:** The section "4.1.2 Core-shell nanoparticles" has been expanded, more information and examples of hydrogels were added. Moreover, section 5 provides more information and examples of magnetic systems associated with hyperthermia.

Line 453: Please, add that the liposomes contain encapsulated doxorubicin.

- **Answer:** At the beginning of this paragraph, liposomes that generally contain DPPC are described. The evolution of these liposomes is then described in the ThermoDox® example, which in turn contains encapsulated doxorubicin. The end of the paragraph has been rewritten to improve understanding.

Through section 5: There are problems with the structure of the manuscript, which make it difficult to read. In sections 4.1.1 and 4.2, preclinical studies had already been introduced. Paragraph 5 again introduces preclinical studies. Please, reorganize section 5 (title and content).

- **Answer:** In the section 4, we include preclinical studies using thermosensitive nanosystems (micelles, liposomes, etc.). Section 5 is about a specific hyperthermia technique (HIFU-MRI), a strategy for guided drug delivery. The title has been changed to make it more consistent.

Line 519: The MR-HIFU abbreviation is being used without definition and introduced later in the manuscript (line 560). Line 522: Please, specify the abbreviation Gd(HPDO3A).

- **Answer:** Abbreviations and their specifications have been added.

Through section 6: Please, specify why no clinical trials are described for the other thermosensitive systems described.

- **Answer:** A paragraph has been added in chapter 6, with another thermosensitive system in the clinical study (lines 688-700).

Please review the abbreviations MR and MRI and unify the abbreviation type where possible.
- **Answer:** The abbreviation MRI was unify.

Finally, it is necessary to make a lot of corrections in the references. I only mention a few examples of the errors: some titles of the articles are missing (e.g. References 14, 27, etc.), some titles are incorrect (e.g. 34), there are striking repetitions in the lists of authors (e.g. 45, 78), in some articles the authors are badly cited (e.g. 42, 78, 79), the newspapers are incorrect (e.g. 47, 63), the DOI (e.g. 44) is missing or the indicated DOI is not correct (e.g. 27, 47, 54).

In summary, I would recommend this work after major revisions.

- **Answer:** All references were re-edited. MDPI recommended that references be prepared with bibliographic software. We used Mendeley, and the MDPI style was acquire from Zotero. The DOI is not included in this style.