To
Ms. Shuang Zhao
Assistant Editor
Pharmaceuticals

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

Dear Editor,

the manuscript has been revised according to the Reviewer’s comments. Please find enclosed the newly revised manuscript containing the changes (highlighted in green). Below, please find a point-by-point response to the Reviewer’s comments.

Reviewer 1

Comments and Suggestions for Authors

The revised version of manuscript entitled “Thermosensitive nanosystems associated with hyperthermia for cancer treatments: a review” by Gomes et al. was improved based on the comments. However, further improvements are required based on following comments:

The title can be revised as “Thermosensitive nanosystems associated with hyperthermia for cancer treatments”, “: a review” is not required.
Answer: As suggested by Reviewer, the title was modified and “a review” was removed.

References are lacking in many sentences. Also, references need to be added to first sentence of the paragraph if few sentences are added from same reference. Add references to the sentences ending in line 66, 70, 71, 76, 80 (page 2); line 128, 148 (page 4); line 249 (page 7); line 261, 271 (page 8); line 334 (page 9); line 355, 358, 368, 383, 385 (page 10); line 397, 416 (page 11); line 435, 452 (page 12); line 468, 473, 502 (page 13); line 517
Answer: All references were included as requested by the Reviewer.

Correct the sentence “…induce to direct cytotoxicity, as well as to lead to…” in line 85 (page 3) as “…induce direct cytotoxicity, as well as lead to…”
Answer: The sentence was corrected according to the Reviewer’s suggestion.

In Figure 1, correct the spelling for “Apoptose” as “Apoptosis” and “Increased drug deliverance” as “Increased drug delivery”.
Answer: Both spelling were corrected in Figure 1.

In line 149 (page 4), revise the sentence “…was shown to have enhanced…” as “…was shown to induce enhanced…”
Answer: The sentence was rewritten as recommended by the Reviewer.

In Table 1, what does “active” mean for response in reference 30, “any evident disease” mean for reference 31?
Answer: “Active” and “evident” were inadequate in this context. Thus, they were excluded in order to avoid misunderstanding.

In Table 1, revise the sentence “…do not increased toxicity…” as “…did not increase toxicity…” for response in reference 33.
Answer: The sentence was revised and the reference was changed to 23.

Correct the sentence “…can be also implemented…” in line 179 (page 6) as “…can also be implemented…” Correct the sentence “…to apply to heat…” in line 205 (page 6) as “…..to apply heat…”
Answer: The alterations were implemented in the manuscript.

Provide full form for the abbreviation RFA in line 230 (page 7).
Answer: The correct abbreviation is RF, thus we changed it in the text.
Rephrase the sentence in line 307-308 (page 9) to make it clear.

**Answer:** This phrase has been rewritten as follow: “Drug targeting systems have been developed specifically for the desired target, which may increase the effectiveness of therapeutic agents and delay the development of resistance”.

Correct the words “described” in line 327 and “reviewed” in line 328 as “describe” and “review”, respectively.

**Answer:** The words were replaced.

Remove word “these” from the sentence in line 407 (page 11).

**Answer:** The word was removed as suggested by the Reviewer.

Revise the sentence “….monomers have shown interesting as a temperature-sensitive material and that are attractive…” in line 412-413 (page 11) as “…monomers are attractive….”

**Answer:** The sentence was rewritten according to the comment’s reviewer. “Polymers synthesized using oligoethyleneglycol (OEG) monomers are attractive alternatives to PNIPAAm with several advantages; the polymers can be synthesized by controlled radical polymerization, have reversible phase transitions, and form effective shields against protein adsorption [75]”.

Add full form for the abbreviation “BGC” in line 425 (page 11).

**Answer:** The information was included in the text.

Correct “P-NIPA” in line 435 (page 12) as “P-NIPAm”

**Answer:** The correction was performed as recommended by the Reviewer.

In Table 2, correct “Docetaxel e Paclitaxel” as “Docetaxel and Paclitaxel”.

**Answer:** The correction was performed as suggested by the Reviewer.

In line 459 (page 12), provide some examples of other stimuli in brackets at the end of the sentence.

**Answer:** Other examples were added such as ultrasound, light and heat
Correct the sentence “…copolymer which DOX…” in line 476 (page 13) as “….copolymer to which DOX…”
Answer: The sentence was corrected.

Replace the word “carrier” in line 502 (page 13) with “deliver”
Answer: We changed the word as suggested by the Reviewer.

Rearrange the words “liposome thermosensitive” in line 625 (Page 17) as “thermosensitive liposome”. Remove the word “to” from the sentence in line 634 (page 17). Replace the word “doxorubicin” in line 648 (page 18) with abbreviation “DOX”. Revise the sentence “…of survival the combination…” in line 682 (page 19) as “….of survival with the combination…” Revise the sentence “…improvements in heating control.” In line 685 (page 19) as “….required improvements in heating control.”
Answer: All the alterations were implemented as suggested by the Reviewer.