Reviewers report

Title: Aerosol drug delivery to the lungs during nasal high flow therapy: an in vitro study

Reviewer: Pierachille Santus

Reviewer's report:

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

The study entitled "Aerosol drug delivery to the lungs during nasal high flow therapy: an in vitro study" represent an interesting in vitro study designed in order to evaluate the possibility to develop an efficient nose-to-lung delivery system in order to overcome the current limitations related to previous studies that have failed, with NHF systems, to deliver substantial amounts of pharmaceutical aerosols to the lungs.

The used substance was a solution of 80% mannitol and 20% l-leucine.

The used device open a clinical question. In particular, is not clear as the HandiHaler (device for DPI) could be use for a pMDI. We don't have an HH device as spray. The used device is a mix between HH and Respimat?

What are the clinical implications and the future improvement? We'll see a change from HH DPI to HH pMDI? Probably should be better to use a device used in real life normally. This point could be better explained and contextualize take in account the current clinical practice.

- The Introduction section must be modify in two points. First, from line 52 to 59: the point is that, not COPD "per se" must be treated with oxygen, but COPD pts with Respiratory failure. So, is the respiratory failure that must be treated with Oxygene. Please better rewrite.

Second, from line 65 to 67: the more frequent COPD infection is not the pneumoniae but the acute exacerbation of COPD. The sentence "Pneumonia can trigger acute exacerbations of COPD" must be delete.
- The primary study outcome/objective should be more clearly rewritten and detailed.

- The conclusion must be implemented with regards to the future clinical applications. Should be underline that the developed system is an "in vitro" model.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

NONE.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal