Proposal for amendment to the Annex 2 of Regulation 2019/6, as advised by the EMA.

First a sincere appreciation of the good and flexible manner this proposal for the Annex 2 has been drafted by the EMA/CVMP and experts.

Please allow me some important comments:

1)

In Title III, 8.1.2 (General requirements for safety for novel therapies), the following text (*in italics below*) is inadequate, refers to a non-applicable legislation, and seems to reflect a theoretical concern only linked to one particular type of novel therapy, DNA-vaccines. This may block development in the field if written into legislation, and a more general text is needed, which can let the specific details be drafted in EMA guidance:

"The requirements of Directive 2001/18/EC should be taken into consideration when the treated animal itself could become a genetically modified organism. While Directive 2001/18/EC applies to finished products containing genetic modified organisms, it remains the best technical guide currently available for listing the necessary data. In particular, a main issue is the integration rate of DNA into germ cells (thus transmissible to offspring) or the potential transmission of the genetically modified cells to offspring. It should also be noted that this problem is not completely the same when considering companion animals and food-producing animals (human consumption of products containing genetic modified organisms)."

It is noted that the last two sentences of the quoted text above, seems based on theoretical concerns since there is no scientific evidence for the occurrence of germline transmission after DNA vaccination, nor for any safety related to human consumption of offspring to DNA-vaccinated animals.

Moreover, having this text under general requirements may cause the topic to be requested for other novel therapeutics without any reason and causing an unnecessary additional burden.

The proposal is therefore to delete the quoted text above and replace it with a general text, e.g.:

"Products containing genetically modified organisms must take into consideration the relevant EU legislation. Further guidance from the Agency on specific topics may be developed and should be taken into account."

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2)

In Title IV, section A.1, the concept of Vaccine Antigen Master File is highly appreciated.

However, for many of the novel biologicals and immunologicals there is an immense research and development ongoing in adjuvants and excipients to improve efficacy and safety of these products, which should be given the opportunity to be protected and to be assessed only once via an adjuvant/excipient Master File system. This will increase the willingness to invest in these important substances, and it will lower the workload for the assessing competent authorities, if the manufacture and control of these substances have already been scrutinized in previous applications.

The proposal is to include in the Annex 2 a **voluntary option for a master file system for excipients and adjuvants.**

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3)

In Title IV, section A.2 Multistrain dossier, the text specifies that the strain/vaccine must be “inactivated”. This normally means that the virus strain is cultivated alive and then killed. However, with the fast evolution of genomic techniques, it may be possible, and safer, in the future to construct the desired strain by other means than grow-and-kill.

A proposal for consideration could be to change the word “inactivated” to **“non-live”** in this section.

Thank you for considering these proposals in the further drafting process.

With best regards,

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