Final AMM Response to the EMA Vaccines Concept paper

- **General comments on the Concept paper on the revision of the Non-clinical and Clinical Module of the influenza vaccines guideline**
    - The Alliance for mRNA Medicines (AMM) is an organization dedicated to advancing and advocating for mRNA and next-generation encoding RNA therapeutics and vaccines for the benefit of patients, public health, and society. Our mission is to propel the future of mRNA medicine, improve patients' lives, and advance scientific knowledge by convening and empowering mRNA industry leaders, innovators, scientists, and other key stakeholders. We welcome and appreciate the opportunity to comment on this concept paper. AMM looks forward to engaging with the EMA in the near future.

Specific comments on text

- **2.1. Introduction**
    - In awarding the Nobel Prize for Physiology or Medicine last month to Katalin Karikó and Drew Weissman, the Committee noted the "impressive flexibility and speed with which mRNA vaccines can be developed pave the way for using the new platform also for vaccines against other infectious diseases. In the future, the technology may also be used to deliver therapeutic proteins and treat some cancer types." We share the Committee's hope for the future of this technology for vaccines and therapeutic uses.
    - We look forward to working with EMA and other international regulators to effectuate the regulatory environment necessary to enable this hope to reach patients as soon as possible.

- **2.2 Problem statement**
    - AMM support's EMA's efforts to "add sections relevant to the development of mRNA-based influenza vaccines" as mentioned in lines 54 and 55 of the problem statement. During the COVID-19 pandemic, mRNA technologies proved extremely effective and flexible in combating the virus.
    - Because the influenza vaccine is updated annually for new strains, this makes it an ideal use for a platform technology such as mRNA. Additional guidance from EMA that address the specific issues pertinent to mRNA will help the field continue to develop.
    - In addition to incorporating sections on mRNA into the influenza vaccines guideline, more broadly AMM suggests the EMA consider regulating mRNA technologies as a "platform technology." This would allow the mRNA community to more quickly bring safe and effective vaccines and therapeutics that can save lives to patients.
    - We also urge EMA to work with other international regulatory who are considering many of these same questions. A clear pathway, harmonized across the globe, is critically important to development of this burgeoning field.
    - A specific regulatory framework for mRNA platforms is needed because the areas in which the field needs clarity for mRNA development and manufacturing are different than the issues most pressing for small molecules and other biologics (including cell and gene

medicine). The development of a specific framework for mRNA would provide certainty for the community as well as EMA as you consider issues from pre-clinical to post-approval.

- The areas where additional guidance is needed include:
  - Consistent data and safety requirements for preclinical and early-stage clinical evaluations with respect to drug substance and drug product (e.g., extracting the full value of previously tested vectors and LNP delivery systems across EMA review divisions) across FDA divisions
  - RNA specific guidance for early clinical evaluation where the same technology is applied in very disparate clinical areas/review divisions
  - Standards and clear guidelines on platform-based human safety data interchangeability can minimize cost and waste of volunteer subject/patient resources in clinical studies, which in turn may lead to improved progress in prophylactic vaccine testing, chronic disease states and facilitate new agents and approvals.
  - The nonclinical safety studies required for a new LNP-mRNA vaccine should be Consistent with WHO guidance "Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations" (2021) and allow for the establishment of a platform approach for nonclinical safety studies for annual seasonal Flu vaccine strain changes. (https://cdn.who.int/media/docs/default-source/biologicals/ecbs/post-ecbs-who-regulatory-considerations-document-for-mrna-vaccines---final-version---29-nov-2021_tz.pdf?sfvrsn=8f57a1af_1&download=true)
  - Examples of topics to address recommendations for assays to evaluate immune responses to neuraminidase and the potential need for clinical endpoint efficacy trials (including choice of controls and success criteria).
- Additionally, next generation RNA technologies, such as self-replicating RNA (srRNA) will also benefit from additional regulatory clarity and harmonization across the globe. Like linear mRNA, srRNA may be best considered as a "platform technology" to expedite effective new vaccines reaching patients, especially in pandemic situations. The specific regulatory questions, around consistent preclinical and early-stage testing, will likely have some areas of overlap and some distinct differences from linear mRNA and thus should be considered alongside but separate from linear mRNA.
- AMM supports further clarification and further investigation on mRNA manufacturing quality control and validation.
  - For example, Lipid nanoparticles (LNPs) play a key role in mRNA vaccines, but there is a risk of high interactions between mRNA and the lipid excipients that are used for the production of the LNP.
- AMM recognizes that the science and applications for mRNA are still evolving and not all regulatory questions can be answered at the moment. We look forward to engaging with EMA on an ongoing basis.

- **2.3 Discussion (on the problem statement)**
  - AMM supports EMA including guidance on mRNA platforms as referenced in lines 61 and 62 of the Discussion section. Designating mRNA as a platform technology will be critical for new or updated mRNA vaccines to reach patients in a timely manner to save or improve lives.

- **2.4 Recommendation**
  - AMM supports the Vaccine Working Party and the ETF updating the current guidelines specifically to include guidance on mRNA technology as a platform technology.
- **2.5 Proposed timetable**
  - AMM supports the proposed timeline, provided that EMA is able to process and thoroughly consider all feedback received within the proposed timeframe.
- **2.6 Impact assessment (anticipated)**
  - AMM agrees with EMA's proposed impact statement and supports the agency's efforts to "guide applicants of innovative vaccines through their product development to licensure" as referenced in lines 95 and 96 of the Impact Assessment Section. A structured framework accelerates the administrative approval process, facilitating quicker evaluations, approvals, and eventual dissemination of groundbreaking therapeutics to the individuals who urgently need them.
- **2.7 Interested parties**
  - AMM agrees with the listed interested parties listed but would ask the Agency to consider foreign medical regulatory agencies, such as the United States' Food and Drug Administration (FDA) and Australia's Therapeutic Goods Administration (TGA) as interested parties as well. While EMA should not be unduly influenced by foreign agencies, regulatory harmonization could expedite patient access to needed therapeutics.

- **2.8 References to literature, guidelines, etc.**
  - Not Applicable

- **Other comments**
  - Because AMM was only officially formed in November 2023, we did not have the opportunity to comment as an organization on EMA's Concept Paper on the development of a Guideline on the quality aspects of mRNA vaccines; the comment deadline was 30 September, 2023. However, we are very interested in this topic and have substantial expertise among our membership. Therefore, we would welcome any future opportunities to discuss this with EMA.