Alliance for mRNA Medicines Response to UK Medicines and Healthcare Products Regulatory Agency (MHRA) Draft guidance on individualised mRNA cancer immunotherapies[1]

The consultation was completed using the online consultation survey.

Regulatory principles

1. Do you agree or disagree with the regulatory principles outlined in section 2 of the draft guidance?

Overall, we agree with the regulatory principles outlined in Section 2. We note that some areas reflected in this guidance will require significant effort from product developers to meet the standards outlined. However, we appreciate the thoughtful approach the MHRA has outlined and believe the principles are relevant and appropriate.

2. The MHRA envisages that in specific circumstances, a highly personalised medicine could be issued with a single marketing authorisation, even where there is a variable component that is tailored to an individual patient's characteristics. Please provide any comments you may have on this approach, and any suggestions for alternative regulatory approaches.

AMM supports the proposal to issue a single marketing authorisation for individualised medicines containing variable components tailored to an individual patient's characteristics. This approach allows individualized medicine to be available without delays to the patient given that the manufacturing process is known and consistent and makes appropriate use of the concept of "prior knowledge."

The variable component should be clearly elaborated in the product design and agreed to by the Agency. If there are any changes on the variable component, a risk assessment should be conducted, and the Agency agreement should be obtained before implementation. Post Approval Safety Studies (PASS, mentioned in Section 7) would provide supportive data on the safety of the medicine.

[1] Guidance accessed online at: https://www.gov.uk/government/consultations/draft-guidance-on-individualised-mrna-cancer-immunotherapies

3. The individualised mRNA cancer immunotherapies are currently classified as Advanced Therapy Medicinal Products (ATMPs), and subclassified as gene therapies. The MHRA acknowledges that the mechanism of action of such therapies is not genome modifying.
    - What are the advantages of such a classification for these therapies across the life-cycle of the product and across different stakeholders?

The advantages include accelerated development pathways to speed up product development, innovation, and market differentiation. Additionally, this approach would provide increased regulatory clarity by tailoring specific guidance to the respective sub-classification taken into account e.g., specific manufacturing, mode-of-action and therapeutic potential.

AMM recommends that MHRA establish a new class, or at least a sub-class if that is more feasible, that is exclusively for mRNA immunotherapies. Since the other subclasses include: a gene therapy medicinal product, a somatic cell therapy medicinal product, and a tissue engineered product, we believe a mRNA immunotherapy would be appropriate and reasonably equivalent as a new class or sub-class.

- What are the disadvantages of such a classification for these therapies across the life-cycle of the product and across different stakeholders?

The disadvantages include additional requirements and longer approval timeline for clinical trial approvals.

We also believe that deciding to not distinguish between genome-modifying therapies (current ATMP classification) and including mRNA medicines within this classification appears likely to cause confusion amongst the general public. Having mRNA medicines treated in the same class of product as genome-modifying therapies may unnecessarily deter some patients from accepting treatment. Therefore, we fully support the MHRA´s considerations for introducing a new ATMP sub-classification for nucleic acids that do not edit the genome.

4. Please provide any additional comments or suggestions you may have on the regulatory principles outlined in section 2 of the draft guidance?

While other regulatory authorities have defined “platform” technologies, MHRA explained why it does not use this term. We believe that as described, the concepts of utilising “prior knowledge” and regulatory classification of individualized medicines to be agreed to on a case-by-case basis are very well defined.

Although it is notable that the draft guidance only indicates use of prior knowledge gained from product manufacturing and references ICH Quality Guidelines Q8 to Q14. Consideration (on a case-by-case basis) should also be given to the application of prior knowledge from nonclinical/ clinical safety data for the development of immunotherapies that use the same fixed mRNA/LNP component for new cancer therapy indications. Some guidance on how such prior knowledge could be used (if justified and agreed with MHRA), for instance, waiving or bridging of nonclinical data; conducting clinical studies of a smaller sample size or conducting PASS, would be very helpful to developers.

Line 118: The manufacturing site could be different if the same manufacturing process and analytical methods used for Drug Substance and Drug Product. If the trial involves multiple countries, there may be several manufacturing sites to support the surrounding regions. In Line 835, it does mention that if multiple manufacturing sites.

Product design

5. Do you agree or disagree with the product design principles outlined in section 3 of the draft guidance?

We are currently unaware of any widely-accepted definition of a neoantigen and therefore suggest that the wording could be changed to “patient-specific tumour antigens” to provided appropriate flexibility.

It is common for neoantigens to be considered only as mutation-based tumour specific antigens. However, they are not always mutation based, and the term is not well defined in the literature. For instance, endogenous retroelements are aberrantly expressed in cancer and these could be considered tumour-specific. Also splicing errors are common in cancers and could also be considered neoantigens. Without defining neoantigen, the guidance is open to interpretation. We do not believe that it is necessary for MHRA to define “neoantigen” at this time, but raise the issue for awareness.

In fact, the guideline is currently limited to neoantigens as targets of an individualized mRNA cancer immunotherapy. AMM suggests broadening the scope of personalized mRNA cancer immunotherapy to include targeting overexpressed tumour-associated antigens as well and not limit to neoantigens only.

We also suggest generalizing the description of the patient sampling procedure. Depending on the indication and/or quality of tumour biopsy, first sampling used to design the personalized product could happen only at the timepoint of tumour removal (through excision or resection). Hence following modifications are suggested for line 197-202:

> *"[..] Patient sampling covers the steps to capture tumour specimens and blood samples. Tumour samples may be collected through biopsies of solid tumours or during tumour removal (through full or partial excision or resection). When a biopsy is performed~~, through a~~ standard care pathway procedures (e.g. needle biopsy or aspiration) should be adhered to. It is essential to ensur~~eing sample~~ the chain of custody, and subsequent accountability for tumour samples throughout the acquisition, storage and manufacturing processes. ~~Section specimen of a full or partial excision of a tumour would be required for subsequent nucleic acid extraction.~~ [..]"*

6. The MHRA proposes that the Product Design aspects of individualised mRNA cancer immunotherapies should be regulated under the medical devices framework, as well as the medicinal products framework. What are your views on this approach?

It is reasonable to have Product Design adhere to requirements of medical device regulations. However, it will be good to clarify that the individualised mRNA cancer immunotherapies are regulated under the medicinal product framework and the Product Design complies with the requirements of medical device regulations.

Regulating the product design aspects under medical device framework will impose an increased burden on regulators and industry due to parallel evaluations of individual product components by different stakeholders, or using diverse platforms.

This proposal is based on the following argumentation:

- The product design steps do not qualify as a stand-alone product. These steps can be considered as a protocol to manufacture the patient-specific mRNA product.
- The intended purpose of the product design steps is to identify, select and arrange tumour antigens (from sequence data of patient tumour) to be encoded by the patient-specific mRNA, which is not a medical purpose.

7. The product design of individualised mRNA cancer immunotherapies may involve the use of an AI/ML workflow. How should the MHRA manage updates and changes from a regulatory perspective?

Section 3.5.2.6 (Product updates) says "Updating iteratively raises a risk that the product moves beyond the boundaries of the validated evidence base and approval. Algorithms utilising continuous learning are not currently compatible with UK medical device regulations and increase the risk of moving beyond the boundaries of the approved and validated evidence."

We recognize that continuous learning systems inherently post some level of risk. However, rather than prohibiting their use, we believe that medical device regulations need to adapt to this scenario. To fully leverage AI, we must eventually embrace systems that continuously learn and improve. With the pace of innovation in this area, it is not in the patient's interest that an AI algorithm be "stuck in time" at the moment of approval. There are certainly ways to ensure transparency and oversight of these outputs before the medication reaches patients.

The Applicant should conduct risk assessment on updates and changes. If it poses medium to high risks on safety or efficacy, the Applicant should send the updates and changes to the MHRA and get the agreement prior to implementation.

8. Please provide any additional comments or suggestions you may have on the product design aspects outlined in section 3 of the draft guidance?

Product manufacturing

9. Do you agree or disagree with the product manufacturing principles outlined in section 4 of the draft guidance?

Overall, we agree with the product manufacturing principles. However, in the drug substance section, several places mention modified nucleotides. The guidance should apply to either conventional mRNA with nucleotide modification or self-amplifying mRNA with natural nucleotides.

But the protein expression in the drug substance release panel is considered not mandatory, as it is considered on the Drug Product release control panel. Functionality on DP includes in addition to the mRNA itself also the functionality of the lipid nanoparticles as delivery system.

Regarding the potency test further guidance is need about the expectation for correlation to biological effect and clinical response, considering the individual nature of the drug product and related responses.

The surface properties testing is rather considered a characterization than a relevant parameter for the release testing panel. Characterization data for the design space of possible constructs, that show, that there is no impact on the surface properties are considered to justify this approach.

10. Considering the individualised nature of the therapies and the need for a rapid turnaround, please provide any comments and/or suggestions you may have on the batch release test parameters outlined in the draft guidance.

11. Please provide any additional comments or suggestions you may have on the product manufacturing aspects outlined in section 4 of the draft guidance?

Line 876 states that Manufacturers should also consider a two-step batch release procedure where critical tests are performed prior to administration. Further specification tests can be completed post-administration. The scheduling for batch release testing should be discussed with relevant regulatory agencies. We have concerns with potential out of specification after the product is administered. If a two-step batch release procedure is considered, further tests can be completed post-administration is for information only.

Non-clinical aspects

12. Do you agree or disagree with the non-clinical aspects outlined in section 5 of the draft guidance?

In general, we agree with the non-clinical aspects outlined in Section 5, but with the following comments.

Line 934-937: It is not clear what need to be done in the second stage to seek to characterise the potential activity and safety of this use of mRNA and the drug delivery system (e.g. lipid nanoparticles). How is this different from what mentioned in the first stage? It later mentions that the second stage of testing should be retained for inspections and could be used in later submissions is also not clear. We request that this section be further elaborated and explained.

The guideline recognizes the limits of testing personalized patient-specific products outside clinical settings. Nonclinical development should use constructs similar to individualized medicine rather than exact batches, emphasizing the importance of representative constructs (or surrogate constructs) in assessments.

13. The exact version of a licensed individualised mRNA cancer immunotherapy product would be tailored to each patient's tumour. The draft guidance recommends **non-clinical studies** using products that are representative of, but not identical to, the individualised licensed product. Please provide any comments you may have on this approach, and any suggestions for alternative regulatory approaches.

14. Please provide any additional comments or suggestions you may have on the non-clinical aspects outlined in section 5 of the draft guidance?

The guidance refers to the World Health Organisation Guidance on non-clinical development of vaccines. We note that the WHO guidance states that "Therapeutic vaccines for non-infectious diseases (e.g. certain cancer vaccines) and monoclonal antibodies used as immunogens (e.g. antiidiotypic antibodies) are not considered here. This presents a contradiction. If MHRA believes the WHO guidance is relevant, we recommend explicitly acknowledging that while the WHO guidance does not apply to cancer immunotherapies, MHRA believes certain aspects of it are in fact appropriate for cancer immunotherapies.

Clinical aspects

15. Do you agree or disagree with the clinical aspects outlined in section 6 of the draft guidance?
We value this approach because it involves applying the same process to each patient, while acknowledging that individual batches will differ from patient to patient.

16. The exact version of a licensed individualised mRNA cancer immunotherapy product would be tailored to each patient's tumour. The draft guidance recommends **clinical studies** using products that are representative of, but not identical to, the individualised licensed product. Please provide any comments you may have on this approach, and any suggestions for alternative regulatory approaches.
17. Please provide any additional comments or suggestions you may have on the clinical aspects outlined in section 6 of the draft guidance?

Post-authorisation aspects

18. Do you agree or disagree with the post-authorisation aspects outlined in section 7 of the draft guidance?
19. Please provide any comments you may have on the proposed requirement of a marketing authorisation for an individualised mRNA cancer immunotherapy to have a requirement for a post-authorisation safety study?
20. Please provide any additional comments or suggestions you may have on the post-authorisation aspects outlined in section 7 of the draft guidance?

Information for patients, healthcare professionals, and the public

21. Do you agree or disagree with MHRA's expectations of manufacturers/developers surrounding around the information to be provided by them for patients, healthcare professionals and the public in section 8 of the draft guidance?
22. At the time of cancer diagnosis, patients may receive lots of information in a short space of time and be asked to make decisions on treatment options.
    - If an individualised mRNA cancer immunotherapy is to be offered as a treatment option, what type of information do you think should be provided to support a patient in their decision making process?
    - If an individualised mRNA cancer immunotherapy is to be offered as a treatment option, what would be the best format for the information provided to support a patient in their decision making process?
    - If an individualised mRNA cancer immunotherapy is to be offered as a treatment option, when is the most appropriate time to provide the information to support a patient in their decision making process?
23. Please provide any additional comments or suggestions you may have on providing information to patients, health and care professionals and the public as outlined in section 8 of the draft guidance.

Supplementary information

24. Please provide any additional comments or feedback you may have on the regulatory approaches to mRNA cancer immunotherapies provided in this draft guidance, and any suggestions for alternative regulatory approaches.

General comments:

- The guideline currently does not clearly distinguish the requirements for different development phases, such as Phase 1, Phase 2, Phase 3, and the requirements for marketing application submission. This poses a risk of overinterpreting the guideline and raises concerns that early development projects may be subjected to unnecessarily stringent requirements.

CureVac proposes to incorporate substructures into guideline and define expectations for each development phase: Phase 1, Phase 2, Phase 3, and marketing application submission.