Medicines & Healthcare products
Regulatory Agency

Draft guideline on individualised mRNA cancer immunotherapies

Contents

Foreword 4
1. Introduction and scope 5
2. Regulatory principles 7
3. Product design 9
3.1. Introduction 9
3.2. Patient sample collection and storage 9
3.3. Genetic sequencing 10
3.4. Bioinformatics 12
3.5. Neoantigen identification and selection 13
3.5.1. Background concepts related to the use of AI/ML 13
3.5.2. Primary Guidance Areas to Consider for the use of AI/ML 14
3.5.3. Additional considerations for the use of AI/ML 16
3.5.4. Regulatory considerations for the use of AI/ML 16
4. Product manufacturing 18
4.1. Introduction 18
4.2. Drug substance 18
4.2.1. Starting materials 18
4.2.2. *In vitro* transcription or synthesis of mRNA and purification 19
4.2.3. Constant and variable elements in mRNA molecule 19
4.2.4. Characterisation of drug substance 19
4.2.5. Process validation 21
4.2.6. Process design 21
4.2.7. Release testing and potency 21
4.3. Drug product 22
4.3.1. Pharmaceutical development 22
4.3.2. Batch size 22
4.3.3. Manufacture of drug product 22
4.3.4. Quality control and batch release testing of individualised batches 23
4.3.5. Stability 24
5. Non-clinical aspects 25
6. Clinical aspects 27

6.1. Introduction 27
6.2. Changes to product design steps 27
6.3. Considerations for randomised placebo-controlled trials 27
7. Post-authorisation aspects 29
8. Information for patients, healthcare professionals, and the public 32
Appendix: List of abbreviations 33

Foreword

The development and impact of mRNA-based vaccines for the COVID-19 pandemic has created new opportunities for mRNA technology. They work by training and triggering the body's own immune system to recognise a pre-defined infection and fight it if found in the body. The immune system will remember this training even if the vaccine is broken down over time. As a result, the body may have long-lasting protection against the infection.

The next generation of mRNA therapies seeks to adapt this method of targeting 'external' infections to tackling 'internal' diseases such as cancer. This new approach works on the understanding that cancer cells have small differences to normal cells. This enables the immune system to be trained to identify these changes and treat cancer cells as if they are external invaders. Like fingerprints, tumour mutations are unique to every patient. Unlike conventional therapies, which are designed for and tested on broad populations, these new mRNA therapies can be personalised to match the tumour fingerprint of an individual patient's cancer. This shift in perspective from treating a broad population to focusing on an individual for the design of a medicine poses complexities in ensuring that such therapies are consistent, safe, effective, and of high quality.

At the MHRA we regulate medicines, medical devices, and blood components in the UK, and we offer this guidance document to provide a clear and comprehensive regulatory framework to support the development, evaluation, and approval of these therapies. It outlines the specific considerations for ensuring reproducibility, standardisation, traceability, quality, safety, and efficacy across the medicine lifecycle, with a focus on the unique challenges. By addressing aspects such as clinical trial design, manufacturing processes, and post-market surveillance, this document aims to streamline pathways for bringing these therapies to patients without compromising regulatory rigour.

The development of these innovative and complex therapies combines expertise from fields such as machine learning, biotechnology, nanotechnology, chemistry, medicine and regulatory science. This requires regulatory frameworks that can adapt to rapid innovations, whilst still prioritising patient safety. As regulators, our priority is to enable innovation while maintaining the highest standards for patient safety and public health. By streamlining development and regulatory review, we hope to facilitate and speed up patient access to these innovative therapies, especially in areas of high unmet need. We aim to make the UK more attractive for the research, development, clinical trials and manufacture of these therapies.

We have written this draft guidance, informed by advice from the independent Highly Personalised Medicines Expert Working Group (EWG) and the Commission on Human Medicines (CHM). While this initial draft guidance document is primarily intended for developers of individualised mRNA cancer immunotherapies, the regulatory and scientific principles discussed herein could broadly be applicable to other disease indications or technologies that could benefit from personalisation or individualisation. Specific cases may be clarified in subsequent updates to the guidance.

1. Introduction and scope

This document is intended to provide guidance on the development and regulation of individualised mRNA cancer immunotherapies that use lipid nanoparticle delivery systems, and the current scope is confined to the specific regulatory and scientific challenges of these technologies. These cancer immunotherapies contain mRNA as the active substance, encapsulated in lipid nanoparticles for drug delivery. The mRNA consists of a fixed component and a variable component. They are individualised because the design of the variable component of the mRNA molecule is tailored to each patient's unique tumour neoantigen profile. Following administration, the mRNA molecule is delivered to host cells for expression of neoantigens, with the aim of generating an immune response against the tumour.

As we acquire experience of different technologies (e.g., peptides, non-integrative DNA, polymer delivery systems) the guidance will be updated accordingly. Moreover, some of the regulatory and scientific principles outlined here will also apply to individualised medicines that utilise other technologies or therapies that intend to treat other conditions including rare diseases.

In the UK and internationally, the term 'cancer vaccine' has been used for certain cancer immunotherapies. From the regulatory perspective of the MHRA and based on definitions in the Human Medicines Regulations (HMRs), individualised mRNA cancer immunotherapies do not meet the definition of vaccines. Therefore, the term 'cancer vaccine' is not used in this guidance.

Due to the novel scientific and regulatory aspects of individualised medicines, developers are strongly advised to seek our scientific advice on their individual product.

Draft guidance on the manufacturing aspects of individualised mRNA cancer immunotherapies is divided into sections on product design and manufacture, encompassing the following steps:

- Product design
    - Collecting tumour tissue and germline control samples from the patient
    - Genetic sequencing to identify tumour neoantigens[1]
    - *In silico* selection of candidate neoantigens
    - Determination of final mRNA sequence including variable region
    - *In silico* screening for potential safety issues including immunotoxicity assessment

- Product manufacture
    - DNA starting material
    - Production of individualised mRNA molecules

[1] Neoantigens are non-self-peptides acquired by tumours which are presented to T-cells via human leukocyte antigen (HLA) antigens on antigen presenting cells e.g. dendritic cells.

- Subsequent standardised manufacturing steps including incorporation into the drug delivery system (e.g., lipid nanoparticles)
- Release of individualised batch for cancer immunotherapy treatment course

Tracking and traceability via a chain of identity will be essential for all manufacturing steps from patient sampling to batch release.

Later sections cover non-clinical and clinical data requirements focusing initially on individualised mRNA cancer immunotherapies. Importantly, there is a section on high-level considerations for the post-authorisation requirements (including the risk management plan). Finally, there is a section on information for patients, healthcare professionals, and the public. This is designed to promote a discussion on the type of information that will be needed to inform a benefit risk discussion between a patient and their healthcare professional.

2. Regulatory principles

Individualised mRNA cancer immunotherapies will be regulated as medicines under the Human Medicines Regulations 2012 (as amended) (HMRs). From the 1st of January 2025, all medicines for human use will be authorised UK-wide following the agreement of the Windsor Framework. For more details, reference should be made to the guidance on UK-wide licensing.

The product design aspects of these medicines will also be regulated under medical device legislation. This is covered in more detail in Section 3 (Product design).

The MHRA envisages that in specific circumstances, an individualised medicine could be issued with a marketing authorisation (MA) under the HMRs, even where there is a variable component that is tailored to an individual patient's characteristics. This means that a single MA could cover use across the target population defined in the indication. The production (including product design process, manufacturing site and process), strength, pharmaceutical form, and method of administration, would be otherwise identical between patient-specific batches. Potentially flexible but predefined processes and controls would be required such that the medicinal product can be reasonably expected to be safe and effective in clinical use. Furthermore, the claimed therapeutic indication would need to be supported by relevant clinical and non-clinical data, as is the case for products with fixed components.

The term 'platform technology' has been used by industry and regulators to describe different scenarios. For example, the European Commission's proposal for a Directive on the Union code relating to medicinal products for human use defines platform technology as:

> 'When a certain process/method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.'

Whereas the US Food and Drug Administration (FDA) draft guidance on Platform Technology Designation Program for Drug Development defines a platform technology as:

> 'A well-understood and reproducible technology … that FDA determines to be appropriate, where the sponsor demonstrates that the technology
> (1) is incorporated in or used by a drug or biological product and is essential to the structure or function of such drug or biological product;
> (2) can be adapted for, incorporated into, or used by, more than one drug or biological product sharing common structural elements; and
> (3) facilitates the manufacture or development of more than one drug or biological product through a standardized production or manufacturing process or processes.'

The FDA definition is broader than the EC definition in that it could encompass products that are not individualised. As there is no defined international consensus on the scope of what a platform technology entails, the term is not used in the remainder of this MHRA draft guidance. Developers however are able to utilise prior knowledge from previous regulatory

submissions as supportive data if justified, and assessed as relevant by the MHRA on a case-by-case basis. References to prior knowledge can be found in the International Council for Harmonisation (ICH) Quality Guidelines Q8 to Q14.

The regulatory classification of an individualised medicine under the HMRs would need to be agreed with the MHRA on a case-by-case basis. The individualised mRNA cancer immunotherapies are currently classified as Advanced Therapy Medicinal Products (ATMPs), and subclassified as gene therapies, under Regulation 2A of the HMRs. Classification as an ATMP allows for a flexible and risk-based approach to regulatory requirements.

It is acknowledged that the mechanism of action of current mRNA therapies does not involve integration into the host genome. Whereas not all gene therapies are designed to edit the host genome, this perceived lack of distinction could lead to overburdensome risk mitigations for this technology as compared to similar technologies such as COVID-19 vaccines. The addition of a new ATMP sub-classification for nucleic acids that do not edit the patient's genome is being considered.

It is also foreseen that mRNA molecules could be manufactured without the need for starting materials produced by biotechnology. Such products would not meet the definition of biological products but could be similar in other respects such that classification as an ATMP would be advantageous. The classification of relevant chemically synthesised products as ATMPs is being considered.

3. Product design

3.1. Introduction

This section covers the activities of patient sample collection and storage, genetic sequencing, bioinformatics (sequence data analysis) and neoantigen identification and selection for the determination of the final mRNA sequences for manufacturing the drug substance.

Each of the activities must be undertaken with care, due diligence, and full forward and backwards traceability between the patient samples and selected neoantigens, as they are critical for the accurate and precise selection of mRNA sequences for the drug substance. The activities in this section are regulated through their respective medical device regulations, as follows:

Activity	Applicable UK Regulations
Patient sample collection and storage	Human Tissue Act 2004 Parts 1, 2 and 3 Human Tissue (Scotland) Act 2006 In Vitro Diagnostics regulation • In Great Britain: UK MDR Part IV • In Northern Ireland: EU IVDR (2017/746)
Genetic sequencing Bioinformatics - sequencing	In Vitro Diagnostics regulation • In Great Britain: UK MDR Part IV • In Northern Ireland: EU IVDR (2017/746)
Bioinformatics - analysis Neoantigen identification and selection	Medical Device regulation • In Great Britain: UK MDR Part II • In Northern Ireland: EU MDR (2017/745)

The applicable medical device and *in vitro* diagnostic device regulations may apply within each activity and the compliance with each regulation would need to be followed. This document describes the principles in the design leading to the target neoantigen selection and does not specify every legislative requirement for devices. Specific legislations will need to be examined in complement to this document.

Traceability must be maintained throughout and between each activity, to ensure the patient sample, corresponding sequence and resultant mRNA selection is linked, using a unique patient identification number.

3.2. Patient sample collection and storage

Patient sampling covers the steps to capture tumour specimens and blood samples. Tumour samples may be collected through biopsies of solid tumours through a standard care pathway procedure (e.g. needle biopsy or aspiration) ensuring sample chain of custody, and subsequent accountability, 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. Currently, the scope of this guidance

does not cover the use of circulating tumour DNA for profiling tumour specific mutations to individualise a medicine.

Whole blood samples could be obtained through phlebotomy or finger prick methods for germline genetic testing. The collection of tumour specimens and blood samples must be undertaken in a healthcare or clinical facility, recognising there are numerous and diverse collection methods and procedures. National guidelines and best practices described by Centres of Excellence should be considered. All methods must be conducted by a trained healthcare professional. Tumour specimens must be quality checked to ensure that a representative section of tissue specimen is obtained, suitable for downstream genetic sequencing procedures.. Duplicate specimen collection is recommended, preferably unstained. Adequate quantities of blood samples should be acquired to support germline genetic testing.

The storage of samples and specimens should ensure that the tissue and blood are viable for genetic sequencing, ensuring nucleic acid integrity. The collected samples and specimens must be stored, transported and retained to enable further processing of the samples in accordance with the provisions of the Human Tissues Act 2004 (or equivalent legislative provisions across the UK) and additional consideration to national requirements. Appropriate consent, codes of practice, consensual analysis of DNA and ethics approvals are expected. Storage of collected samples and specimens shall be governed by procedures that preserve sample integrity for genetic material extraction. For example, storage of tumour specimen may be chilled, frozen, in equivalent nucleic acid stabilisation solutions, or in Formalin Fixed Paraffin Embedded (FFPE) blocks or curls for preservation, storage and transportation. Whole blood must be uncoagulated by preservatives and anti-coagulants that do not interfere with nucleic acid extraction methods. Cleaned and fresh starting material is often preferred for sequencing to prevent inhibition from contaminants. If samples are frozen and thawed, a fresh-frozen study would be expected to characterise the sample stability. Where applicable, the use and effects of proprietary preservation reagents must be characterised and validated to understand their impacts on nucleic acid sequencing.

A standardised and consistent protocol is expected for the collection, storage, and transportation of tumour specimen and blood samples, in line with standard pathology practices. Where multiple healthcare facilities are employed, robust quality control procedures must be established and adopted to ensure consistency across sites assuring specimens and samples are viable for nucleic acid extraction and sequencing. Sample quality cut-offs procedures will need to be implemented to prevent sub-optimal blood samples and tumour specimens from being progressed through into genetic sequencing through specification of minimal tumour content acceptance quality criteria. Sub-optimal samples or specimens must not be used for generating neoantigen identification and selection. A morphological quality control is recommended to ensure the tissue contains the target population of cells for genetic sequencing.

3.3. Genetic sequencing

Genetic sequencing covers the steps for sample amplification, library preparation, and sequence analysis. There are numerous sequencing instruments, and each sequencing

technique requires different sample preparation protocols. The type of sequencing should be documented and rationalised for the relevant patient sample type.

Sample preparation covers the steps required to transform mixtures of nucleic acids from biological samples into different types of libraries suitable for sequencing. Samples must be examined and inspected before extraction of nucleic acids. Inspections must be undertaken to examine sample contamination and signs of improper storage. Whilst sample preparation varies depending on the type of genetic material (DNA or RNA), the quality of the sample will depend on several factors. Such factors should be assessed, and mitigating actions adopted to optimise genetic material extraction. Appropriate sample preparation protocols should be documented, adopted and followed.

Each step of the sample preparation procedure requires different considerations depending on the type of sample and sequencing instrument employed. Protocol and sample preparation methods and controls should be validated and optimised before starting patient sample analysis to ensure the highest quality results. Sources of contamination should be minimised through the separation of designated workspaces.

The extraction of nucleic acids should consider the most optimal methods for obtaining pure DNA or RNA. The sources of the nucleic acids being extracted in the tumour specimen should be fully understood – that is the homogeneity of the population of cells from the specimen. Whilst white blood cells from a blood sample are relatively homogenous, needle biopsy samples of a small tumour sample would be difficult to isolate. Therefore, a characterisation of the homogeneity of the samples is required.

Nucleic acid extraction procedures as defined by the manufacturer of the sequencing instrument should be followed. Deviations must be minimised and fully considered with strong rationales identified for the deviation from the manufacturer's instructions. Care should be given to avoid contaminants, such as haemoglobins or residual formalin from FFPE specimens. Insufficient proteinase treatment leading to carry over proteins and sample cross-contamination require quality checks to be undertaken. Amplification may be performed if instructed by the manufacturer of the sequencing instrument, in which case any mitigations of bias must be rationalised and documented. The use of IVD or diagnostic sequencing instruments is preferable and Research Use Only (RUO) sequencing instruments should be avoided unless a validation is conducted for diagnostic/IVD application. The requirements for the sequencing instrument including the software in secondary analysis must be validated to meet Good Manufacturing Practice (GMP) requirements.

Sequencing library preparation is a very important step before sequence analysis. Where possible, commercial kits should be used and would be preferred. Care must be taken on the quality of various commercial kits for clinical diagnostic use. Development of own-proprietary sequencing libraries should be avoided. Appropriate library quantification should be considered to ensure high quality sequencing data — the technique adopted should be fully described with rationales provided. Bias associated with sequencing libraries should be understood and mitigated, ensuring the number of unique nucleic acid sequences present in the sample are optimised. A standardised and consistent technique could be adopted for the preparation of sequence libraries to remove variation across repeat library preparations. Quantification should be undertaken for quality control of the libraries for optimal library concentration using quantitative polymerase chain reaction

(PCR) or digital PCR (quality methods and optimal fragment length using electrophoretic methods). Sequence bioinformatics should be conducted on the software recommended by the commercial manufacturer of the sequencing instrument. The sequence analysis software should be computer systems validated to meet GMP requirements for software, for example against Good Automated Manufacturing Practice (GAMP) categories, to assure patient safety and data integrity.

3.4. Bioinformatics

Bioinformatic analysis is crucial for distinguishing tumour-associated gene variants from germline variants. It is recommended to conduct a thorough quality check to separate germline variants and enrich tumour-associated gene variants for selecting neoantigen candidates.

Implementing thorough quality control assessments and maintaining an optimised and validated bioinformatics data analysis pipeline is critical to obtaining statistically significant and reproducible results. Once the raw data is generated from genetic sequencing, software tools should be utilised to evaluate quality metrics such as read quality, coverage and read depth. It is important to ensure that the read quality and read depth are adequate for analysis and not below the cut-off Phred quality score limit (≥30 accuracy 99.99%) for quantitative analysis. After analysis, the next stage involves identifying and ranking potential neoantigen candidates to be included in the final mRNA sequence.

In general, bioinformatics data analysis consists of three major steps:

- Primary, which involves sequencing, base calling, preliminary analysis of raw data, quality control and filtering based on Phred score and mapping to the reference genome;

- Secondary, which involves variant calling from the mapped bam files and filtering of called variants based on quality thresholds such as Genome Analysis Tool Kit-Variant Quality Score Recalibration (GATK-VQSR) analysis; and

- Tertiary, where artificial intelligence (AI) and machine learning (ML) models are used to filter and select neoantigens.

The Bioinformatics software pipeline should be accredited by External Quality assessment (EQA). Bioinformatics pipeline is typically in an ongoing development. Therefore, both the software and the pipeline need to be validated with every version update, either as standalone programs or integrated pipeline. It's crucial to document analysis parameters and maintain a pipeline run log to ensure reproducibility. The analysis and variant calling should adhere to industry best practices like those recommended by GATK. Any software, whether developed in-house or externally, must undergo rigorous quality checks following any modifications (e.g., adjustments to ranking criteria or changes to expression thresholds). These checks are essential to maintain consistency and reproducibility across cohorts and ensure the reliability of the data analysis. Documenting changes and validating the software after updates are critical

steps in preventing discrepancies in outcomes. Additionally, a clear statement for data storage and its lifecycle should be established and documented.

Bioinformatics data is subject to qualifying consent, and the results of the analysis used solely for a specific intended purpose (refer to the Human Tissues Act 2004 section 45(1)(a)). The IT infrastructure hosting or storing the data and the data itself will need to be secure and the risk from security vulnerabilities assessed, which will need to be documented along with validated mitigating actions. Interpretations, algorithms, computational methods, statistical techniques, and analysis outputs using software that determine a prediction or absolute result that can be used for a medical purpose is regulated as a Software as a Medical Device (SaMD). Bioinformatics pipelines often rely on multiple dependencies, which should be clearly catalogued and subjected to thorough risk assessments. This ensures transparent reporting of the functionality and limitations of any integrated artificial intelligence and machine learning (AI/ML) components. Such transparency is vital for maintaining accuracy, reproducibility, and regulatory compliance in bioinformatics analysis.

3.5. Neoantigen identification and selection

This section covers the concepts and considerations for developers when using artificial intelligence/machine learning (AI/ML) for the identification and selection of neoantigens to inform the product design. Identification of candidate neoantigens is based on the output data from the bioinformatics pipeline activities occurring prior to this identification and selection stage. Furthermore, best practice principles outlined in the bioinformatics section should be maintained where applicable, to ensure processes achieve aligned standards.

Other software methods for neoantigen identification and selection may be utilised; however, product safety regulations remain universally applicable. For the purposes of this document, AI/ML technologies will be considered subject to the regulations governing SaMD. The computational analysis of neoantigens often involves a range of techniques including AI/ML. More broadly, the scale and complexity of the data aspects of genomics and bioinformatics activities, often aligns with the advantages of an AI/ML approach to activities such as neoantigen identification. Therefore, this guidance focuses on AI/ML to recognise the future direction of travel of this rapidly evolving area.

3.5.1. Background concepts related to the use of AI/ML

AI is a broad term that covers many different approaches to creating engineered systems that generate outputs such as content, forecasts, recommendations, or decisions for a given set of human-defined objectives. However, to date there is poor global consensus on definitions and categorisation of AI/ML, making it challenging to ensure all stakeholders are aligned when discussing the use of AI/ML within in specific domain. Choosing the most appropriate type of AI technique (also known as algorithm model) will depend on parameters including the specific functionality of the task, the importance of factors such as insights to the AI/ML decision making process, data, and commercial constraints. This section provides a high-level background and context to the use of AI/ML within complex workflows and systems (such as in neoantigen selection). This is to highlight that the insertion of an AI/ML tool into poorly

controlled and unvalidated workflows has potential to increase risk and obfuscate failures which can have serious downstream consequences. However, when appropriately understood and managed, AI/ML possesses the potential to improve workflows and patient outcomes.

3.5.2. Primary Guidance Areas to Consider for the use of AI/ML

To guide the use of AI/ML technologies and models in neoantigen selection, the following aspects are key areas that require consideration and detailing in the development and maintenance of these tools for neoantigen identification. A body of AI in healthcare guidance and standards has emerged in recent years. Good Machine Learning Practice (GMLP) guiding principles from the MHRA, US FDA, and Health Canada will give readers a foundation for AI/ML development. In addition, structured frameworks exist to guide the development and management of AI systems, specifically focusing on those that employ machine learning, including ISO/IEC 23053. A comprehensive list of AI development standards can be found from the AI Standards Hub.

3.5.2.1. Performance factors

AI/ML performance (e.g. accuracy, reproducibility, repeatability, and stability) relates to data (e.g. quality, quantity, and appropriateness). For AI/ML, data can be analogous to being the raw material used to create a model. Therefore, as with many statistical techniques, the relationships between the data used for training any specific AI/ML model and the target variables are key to a well performing AI/ML product/tool. These data-AI/ML relationships have several dimensions to consider, such as the number of target variables, the spread of values within a target variable (variance), the prevalence or quality of values and any relationship between variables or thresholds. Such considerations are commonplace and are broadly applicable risks to manage in many workflows. The purpose is to highlight the degree to which AI/ML models are sensitive to these variables and some of the limitations on mitigating the risks present.

For neoantigen selection, the AI/ML would form part of the bioinformatics pipeline. Broadly, the AI/ML receives the sequenced genome of the stored patient sample, and outputs the potential neoantigens for downstream mRNA production of an individualised medicine. The target variables (and associated considerations) are outlined in the genetic sequencing section and can be further influenced by variations upstream from sequencing during the sample collection and storage stages. Generally, the number of variables and/or greater variation of variables within the system you are building the AI/ML for, the harder the data set challenges. Sufficient representation of these variables (and known variance within variables) is required to produce an accurate model. For neoantigen identification by AI/ML, ensuring that the range of relevant biological factors (e.g. cancer types and immunogenicity) sample collection differences (e.g. tumour location vs blood samples) and genome mapping technique differences, need to be captured in the data used to train and verify the AI/ML. This background is provided to give context to some of the risks stemming from poor and/or unreliable performance of AI/ML in clinical and scientific areas with highly complex, numerous and inconsistent variables. All processes prior to the AI/ML step in the mRNA manufacturing process must be sufficiently validated, controlled and

represented in training data to minimise the risks such as bias and over/under-fitting of the algorithm model. Furthermore, developers should put in place systems to record which 'version' of the AI/ML performed the neoantigen selection for each batch of the therapy (to include documentation on the training data sources and other software dependencies). The assessment of such AI/ML systems should be undertaken by an appropriate organisation.

Note that acceptable levels of accuracy of preceding steps in the workflow may have significantly different requirements for an AI/ML than what may be acceptable for a human operator. Therefore, sufficient validation activities of the steps that precede the AI/ML model must be conducted with respect to the requirements of the AI/ML which may differ from previously human orientated gold standards. For example, the differences in reagents, equipment and data quality may not be impactful to a trained human operator who can compensate for some differences even such differences have not been seen before. However, the ability for an AI/ML to handle inputs from outside its training dataset range is a parameter that must be built for and validated specifically. The extent to which an AI/ML model can manage these new inputs is often referred to as generalisability.

3.5.2.2. Generalisability vs Narrow Focus

Generalisability as a feature of the AI/ML needs to be considered as a design requirement and is pertinent to the risks the AI/ML can bring to the workflow. For example, there is typically a tradeoff between generalisability and local accuracy for a more constrained set of inputs. This must be balanced and considered for AI/ML development approaches, considering the specific context of use. Stakeholders assessing the safety and reproducibility of the neoantigen selection process need to understand and validate not just the type of AI/ML but the approach taken around the data inputs for any given model. There must be consideration of whether the AI/ML produces a single model from sufficient training and test datasets, that performs appropriately across different sequencing methods to be safe and effective, i.e. it can act as a "generalised" model. Alternatively, multiple models or combination of models may be used collectively as part of the workflow to optimise outcomes. These may be validated separately or collectively.

3.5.2.3. Performance Drift

Throughout the lifecycle of the development and use of AI/ML models, performance drift may occur. Processes must be in place to monitor performance. Any aspects of calibration and tuning (e.g. retraining or parameter adjustment activities) should be detailed to ensure the maintenance of adequate performance. This applies to both unintended performance changes caused by environmental factors and intended performance changes, such as design updates or modifications to design processes.

3.5.2.4. Bias

Whilst the general concept here is of a individualised approach and product development, the model development prior to this will likely be based on existing datasets taken from certain patient population cohorts. It will be necessary to

ensure that these datasets are representative of the intended population for whom these individualised medicines are being developed.

3.5.2.5. Transparency

Beyond the upstream process and data considerations that impact the performance of the AI are risk considerations relating to validation and understanding of the internal model processes. This may be referred to as model transparency and is sometimes referred to as “Blackbox” AI. The extent to which stakeholders can determine what parts of the input data the AI is using to produce an output is model dependent. This relates to the underpinning architecture of the model and any features designed into the model to assist with understanding. How transparent and understandable a model is, is a crucial feature to the level of validation needed and to conducting analysis during failure model analysis and correction.

3.5.2.6. Product updates

Product updates (including algorithms used in the pipeline) must adhere to safety and performance requirements. Software developed in-house or otherwise should comply with quality checks upon any modifications made to it, to retain consistency across the cohorts in use. Product updates can be required to maintain performance and safety within the validated and evidenced intended purpose. 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.

3.5.3. Additional considerations for the use of AI/ML

In addition to the primary points on performance, generalisability, drift, bias, and transparency, there may be further considerations to ensure the safe and effective use of these techniques. These include features such as the multi-disciplinary expertise required for this work, the requirement for good software and cybersecurity practices, the importance of data privacy and ethical considerations and an understanding of any interactions between humans and the performance of the AI/ML tools. Many of these principles have been captured in the GMLP guidance, co-produced by the MHRA, US FDA, and Health Canada.

3.5.4. Regulatory considerations for the use of AI/ML

As the scientific development of AI/ML continues in this context of medicine development lifecycles, as outlined above, it is necessary to consider the accurate regulatory status and strategy for the use of AI/ML here.

A recent reflection paper from the EMA, published in September 2024 highlights the need to further consider the regulatory interactions across the existing legislation for medicines, *In vitro* diagnostic and general medical devices. For the purposes of the UK, this requires us to consider both legislation for GB and the EU legislation that applies in Northern Ireland. Such regulatory considerations significantly apply to the

AI/ML tools, during clinical trial and live production stages of their use. It is prudent to begin with an early consideration of the proposed regulatory strategy for these AI/ML products, and to continue to monitor and engage with the development of any regulatory guidance in this area.

Depending on the exact techniques and processes used, alongside jurisdictional legislations and interpretations, the AI/ML tools used may qualify as part of the regulated requirements of GMP processes for medicines, or as SaMD, either under the general medical device legislation or under IVD legislation. This may need to be assessed by a conformity assessment body as applicable. For example, software that analyses genetic data to match a patient to a specific treatment, predicts the suitability of certain treatments, or creates an individualised treatment based on the patient's biodata, would fall under the medical device regulations. This includes applications such as identifying specific genetic mutations linked to drug response, pinpointing disease drivers, and identifying therapeutic targets through software. Any changes or updates to such software would require an assessment of the nature/extent of change and if required, a reassessment of the software. However, whichever regulatory route is used or required for the use of AI/ML in this context, the above principles and points of guidance will be equally necessary and valuable to be considered.

References to relevant published guidance documents are provided below:

- Regulating medical devices in the UK
- In Vitro Diagnostics
- Notify MHRA about a clinical investigation for a medical device
- Register medical devices to place on the market
- Software and artificial intelligence (AI) as a medical device
- Good Machine Learning Practice for Medical Device Development: Guiding Principles
- Predetermined change control plan for Machine Learning
- AI Standards Hub - The New Home of the AI Standards Community
- ISO/IEC 23053:2022 - Framework for AI systems using machine learning
- ISO/IEC 22989:2022 - Information technology — Artificial intelligence — Artificial intelligence concepts and terminology

4. Product manufacturing

4.1. Introduction

The chemistry, manufacturing, and control of the product is regulated under GMP. The manufacture of products for use in clinical trials and subsequent commercialisation must be carried out at a site that holds an authorisation for the manufacture/importation of investigational medicinal products for human use (MIA(IMP)) or a licence for the manufacture/importation of licensed medicinal products for human use (MIA), if based within the United Kingdom.

The active substance is the mRNA, and the drug product is the formulated active substance, that is the mRNA delivered by an appropriate drug delivery system. The mRNA could be encapsulated or complexed with the drug carrier system, depending on the design of the formulation.

A clear production batch definition is required from tissue sampling to the labelling of the final container to ensure consistency and traceability is maintained throughout, especially the design and manufacturing cycle of the drug.

A quality by design (QbD) approach should be taken. The design space principles described in ICH Q8 and Q14 could also be applied. References to other relevant published guidance documents are provided below:

- The MHRA Orange Guide
- The MHRA Green Guide
- The Human Medicines Regulations 2012
- The Human Medicines (EU Exit) Regulations 2019
- The Medicines for Human Use (Clinical Trials) Regulations 2004
- The Medical Devices Regulations 2002
- Medicines and Medical Devices Act 2021
- EudraLex Volume 4

Specific considerations are provided below to help support development of a commercial manufacturing process and application for marketing authorisation.

4.2. Drug substance

4.2.1. Starting materials

The starting material(s) will be defined and justified by the manufacturer. Generally, such starting materials are expected to be the nucleotide substrates from which the mRNA is manufactured. Currently this could include a DNA plasmid and ribonucleotides. Direct synthesis of the mRNA would only require the ribonucleotides to be defined as starting materials. Controls for the starting material should be stringent and well-documented. The principles of GMP will apply to the manufacture of starting materials for individualised mRNA immunotherapies, principally risk-determined controls and regular QP audits (for example the 'Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products' and the 'Questions and answers on the principles of GMP for the manufacturing of starting

materials of biological origin used to transfer genetic material for the manufacturing of ATMPs' may apply). The manufacture of starting materials should be performed by a site holding a manufacturing licence as this is the start of manufacture for an ATMP. In instances where the manufacture of the patient-specific batch requires a starting material common to all the batches, this would likely require GMP certification. An example would be the use of master and working cell banks for the manufacture of a starting material; where sites establishing or storing such cell banks, virus seeds or other associated starting material are expected to hold a GMP certification, and if the site is in the UK a MIA. The requirements for demonstrating GMP compliance of starting materials should be discussed with the relevant regulatory authority.

4.2.2. *In vitro* transcription or synthesis of mRNA and purification

A detailed description of the manufacture of the active substance from the starting material(s) should be provided. The *In vitro* transcription or synthesis of the mRNA and its purification should be described along with operating parameters, in-process controls and acceptance criteria. Any intermediate products and critical steps should be defined. Any hold steps and transportation should be described and suitably validated. If there is storage of the drug substance, the container closure system and storage conditions should also be described in detail and suitably justified.

The equipment and premises should be qualified for aseptic manufacture of the product. They should be designed with engineering and procedural controls to avoid cross-contamination between the patient-specific batches. The use of product-specific and single-use equipment is recommended wherever possible. Appropriate cleaning processes should be applied and demonstrated for shared equipment when use of single-use equipment is not possible.

4.2.3. Constant and variable elements in mRNA molecule

It is expected that the mRNA sequence elements encoding the neoantigen peptides will be highly variable between patients. They may also impart differences in the total mRNA length. The risk to the manufacture of the active substance from sequence variation will need to be continuously assessed and updated as knowledge expands. The manufacturer will have to demonstrate that the process is under control and that the final product meets the specifications for the expected range in mRNA length, sequence, and structure. The capabilities of the manufacturing process will need to inform the sequence design in the product design in order that every batch is manufactured under adequate control.

Other than the neoantigen sequence elements, the mRNA is expected to consist of constant elements that perform functions typically related to expression, as well as affecting the stability of the drug substance. These will be constant between patient batches.

4.2.4. Characterisation of drug substance

The characterisation of the drug substance should encompass all components present in the finished product. As some parameters may not be possible to be tested

for release for every batch, the characterisation of the drug substance and final drug product during development is considered critical for the individualised immunotherapy product. The characterisation studies aim to provide an adequate understanding of the active substance and final product. Experimental data are likely to be necessary for the mRNA drug substance alone and for the formulated mRNA drug product.

The characterisation data should cover the expected range of mRNA lengths and structures. Heterogeneity in the product sequence should be considered as part of the characterisation studies, including incorporation of modified nucleotides. The expected range of heterogeneity should be studied, as well as the physicochemical properties of the mRNA drug substance and the encapsulated mRNA in the drug delivery system. The effect of modified nucleotides on mRNA attributes such as structure and stability should be characterised. The morphological characterisation of the mRNA encapsulated inside LNPs would be expected during development, so that an understanding of the potential differences when changing to a different mRNA sequence can be demonstrated.

Consideration of the variation in mRNA sequence at the neoantigen elements should be included in the characterisation. This could be an expansive characterisation at the *in silico* level with selective experimental studies. Sequence characterisation should consider the effects on secondary structure and other potential interactions from variation. Since not all sequences can be fully characterised prior to a marketing authorisation application, the use of design space principles is recommended.

Non-mRNA components should be characterised in the context of their required function in the finished product. This is expected to include, but not limited to, various lipids, polyethylene glycol (PEG) derivatives, cholesterol, and polymers which should be characterised in chemical and physical terms. They should also be characterised with regard to encapsulation of mRNA, interactions with the mRNA drug substance and their role in the mechanism of action such as cell uptake and delivery. Any qualitative and quantitative studies performed should be appropriately justified. Interactions with the immune system may also need to be addressed in characterisation. This may complement the pre-clinical data to support understanding in the uptake and biodistribution of the drug product. Where multiple mRNA drug substances are incorporated, any impact on the critical quality attributes (CQAs) should be investigated.

The characterisation should establish the required CQAs and controls for the release of the active substance and finished product that are applied to every batch. These will also form the basis for the comparability analysis when developing the manufacturing process or establishing new manufacturing facilities. With sufficient characterisation of quality attributes, it is possible to explain and justify any differences observed during the comparability analysis. Otherwise further clinical and pre-clinical studies may be required. The use of prior knowledge as supportive data can be used where justified as relevant based on the similarity of attributes.
Any potential impurities from the manufacturing process should be characterised in the context of the risk to patients at administration, including both immunogenicity and reactogenicity. The interactions of impurities with the active substance and final product should also be considered. A robust strategy for eliminating unnecessary

impurities should be in place; an appropriate risk assessment for the control of impurities can be considered.

4.2.5. Process validation

The entire manufacturing process should be validated prior to commercialisation. This should include the *in vitro* transcription, purification, hold steps, drug substance formulation, filling, packaging and transportation. The validation data should demonstrate that each step of the process is under control regardless of variation in the starting material. Critical steps and controls in the manufacturing process should be defined and validated. Representative mRNA with characteristics comparable to the patient-specific mRNA sequences could be used for validation purposes.

The validation should cover the expected range of mRNA lengths and sequence variation for the patient-specific manufacturing batches. A minimum of three representative mRNA batches will be required. More may be necessary to cover the expected variation and—if applicable—fulfil the principles of a design space. The establishment of a continuous process verification system alongside the commercial manufacturing process is recommended in order to capture knowledge from further batch production and improve the process post-authorisation (see ICH Q7).

4.2.6. Process design

Process design studies can make use of prior knowledge from similar products to establish controls and parameters for manufacture during development. The applicability of data from similar products to the process design will be dependent on the overlap in quality attributes and the scale of manufacture. The manufacturing controls for the commercial manufacture will need to be validated for the product using representative batches.

4.2.7. Release testing and potency

The specifications define the active substance regardless of variation in the starting material. Wherever possible, the active substance, and final product should be subject to release testing. It may be acceptable to omit release testing for the drug substance if justified and authorised, but exhaustive control is expected at the drug product level. Some release testing might not be possible on the formulated drug product for technical reasons, so testing at the drug substance level will be required.

A typical set of mRNA drug substance tests could include appearance, particulates, pH, endotoxin, bioburden, entire nucleotide sequence, RNA concentration, capping efficiency, poly(A) tail, mRNA integrity, mRNA purity, residuals (which may be template, enzymes, solvents, and nucleotides), and the functionality of the desirable mRNA drug substance (e.g. protein expression). Where applicable, pharmacopoeial limits should be adopted. This is not an exhaustive or prescriptive list, but it will depend upon knowledge of the CQAs determined through characterisation of the concerned drug substance and drug product. These tests may be used at release or subject to in-process controls. The acceptance criteria for specifications will be set using knowledge of the manufacturing capability and clinical experience.

Potency is the quantitative measure of biological activity based on the attribute of the product linked to the relevant biological properties. The potency assay should be based on the intended biological effect and ideally related to the clinical response. This is expected to be a challenge for individualised mRNA neoantigen immunotherapies. It is possible to justify the use of a potency assay that measures a product attribute that has been demonstrated to correlate with the intended biological effect. An analytical method that measures a correlate – such as protein expression - is considered a functionality assay rather than a true potency assay. The use of physicochemical measures, as a functionality test, in place of a cell-based expression assay need to be substantiated with adequate data to support biological correlation. The complex mechanism of action for mRNA neoantigen immunotherapies may require multiple potency/functionality assays. It is recommended that these are established as early as possible in development. Preferably a validated potency/functionality assay will be available for testing batches in the pivotal clinical trial.

The analytical methods should be validated and adhere to ICH Q2 for the control of the commercial manufacturing process. They should provide an adequate measure of attributes to determine comparability between clinically qualified material and the batches manufactured with the commercial process as per ICH Q5E.

4.3. Drug product

4.3.1. Pharmaceutical development

Prior knowledge gained from mRNA products with the same administration route may be pertinent to the product development and can be used as supporting evidence in choices in the final product design. The effect of the variation in mRNA sequence, length, and structure on drug loading by the intended drug delivery system, physicochemical properties of the drug carrier (e.g. nanoparticles), release, and subsequent cellular uptake and translation should be considered in detail.

4.3.2. Batch size

Each batch is patient-specific but nevertheless is expected to be within the validated range and subject to the same manufacturing controls. The manufactured product is a batch.

A clear production batch definition is required from tissue sampling and drug product intermediates to the labelling of the final container to ensure consistency and traceability. To ensure the individual patient batch is linked to the individual patient sample, a protocol for chain of identity and chain of custody should be implemented that uses a unique patient identification number.

4.3.3. Manufacture of drug product

The drug delivery system protects the mRNA from nuclease degradation and enables its entry into cells for expression of the neoantigen peptides. The components of the drug delivery system are considered excipients. They should be of pharmacopeial quality where monographs apply, described in detail, justified in terms of their inclusion and levels, and subject to stringent controls. Where novel excipients are

employed, the synthesis and controls, as documented in a similar manner as in an Active Substance Master File (ASMF) should be provided. The required non-clinical studies supporting the use of novel excipients must be performed and presented. The incorporation of the mRNA active substance with the drug delivery system is part of the manufacture of the drug product. A detailed description of the manufacture of the finished product - from the active substance and excipients to the formulation with the drug delivery system - should be provided, along with the required in-process controls, supported by relevant process validation data. For individualised medicines, this process may have been established based on prior knowledge from various mRNA with similar lengths, sequences, and structures and identical drug delivery system for the intended route of administration.

In addition to the conventional physicochemical characterisation of the drug product, which includes, but not limited to, particle size distribution and polydispersity (e.g. for nanoparticle encapsulated mRNA), surface properties (including charge) and morphological characterisation, the characterisation of the drug product may require studies of the drug delivery system components to adequately understand the interactions with the mRNA, any impurities and anticipated interactions *in vivo* (for example, the formation of RNA-lipid adducts where LNPs are used as the drug delivery system).

Where hold-time or temporary storage are required for drug product intermediates, these should also be adequately validated and controlled within the agreed conditions. Subsequent filling and packaging process should also be detailed, supported by relevant validation and stability data. The equipment and premises should be qualified for aseptic manufacture of the product. They should be designed with engineering and procedural controls to avoid cross-contamination between the patient-specific batches.

If multiple manufacturing sites are required for different batches, these sites should be appropriately validated with the commercial process to ensure comparability of the product manufactured at different sites.

4.3.4. Quality control and batch release testing of individualised batches

This needs to be immediate to meet an acceptable turn-around time. The proposed release specification should be determined based on pharmaceutical development data, as well as relevant stability data from process validation and clinical batches. Appropriate risk assessment on the process and controls can be made. Where data from medicinal products with similar properties that use the same manufacturing process are available, these may be used in support of the control strategy. Additional product-specific data is required to establish the acceptance criteria. The release testing may include, but not limited to appearance, pH, osmolality, particulates, identity of the mRNA drug substance, RNA concentration, mRNA purity, residual solvents, lipid impurities, and potency/functionality assay(s).

The specific quality considerations of the drug delivery system, those that are CQAs determined by characterisation, will need to be included in batch release testing.

These include particle size and distribution (polydispersity), surface properties, mRNA encapsulation efficiency and product-related impurities (such as RNA-lipid adducts). The omission of CQAs from drug product release testing may be authorised, where justified by sufficient manufacturing data to demonstrate in-process control. These omissions may be supported by extensive characterisation data. The drug product release will require endotoxin and sterility testing. Any deviation from pharmacopeial standards on testing should be discussed with the relevant regulatory authority prior to submission. Where applicable, pharmacopoeial limits should be adopted for the drug product specifications.

Testing for the absence of adventitious agents should be performed using the analytical procedures described in the British Pharmacopoeia (BP)/European Pharmacopoeia (Ph. Eur.). Where the required turn-around time is prohibitive for the testing of absence of adventitious agents under the pharmacopeial methods alternative validated testing may be acceptable. The manufacturing process should be designed to minimise the risk of contamination including through control of the starting materials, raw materials, and excipients.

A critical set of tests for release that can be performed in the restricted time prior to clinical use must be defined and justified for the drug product (and possibly drug substance). The amount of material available may also restrict the tests that can be performed. Otherwise, additional samples should be stored for further analysis. 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.

4.3.5. Stability

A shelf-life for any intermediates (if required long-term storage), or hold-time for short-term continuous manufacturing process, the active substance and finished product should be defined. An in-use shelf-life and conditions should also be considered. Storage conditions, including the freeze-thawing steps, if applicable, and transportation should be supported by relevant experimental data.
The container closure system should be described and its compatibility with the product demonstrated.

Real-time stability data is required to justify shelf-life claims as per ICH Q5C. The collection of data on temperature excursions, photostability, transportation and other in-use clinical scenarios is recommended. The entire cold-chain storage through manufacture, temporary and long-term storage to in-use storage should be incorporated into stability study design.

5. Non-clinical aspects

Development of individualised mRNA cancer immunotherapies should take into account concepts in the ICHS9 Guideline on non-clinical evaluation for anticancer pharmaceuticals. In line with this, separate dedicated testing for certain aspects in animals (e.g. safety pharmacology, reproductive toxicology) are not expected. Developers should also take account of guidance from the World Health Organisation on Non-clinical development of vaccines; however, allowance should be made for the differing nature of the type of use intended for patients with cancer.

In principle, a product to be used will be based on a construct, that is, an mRNA insert encoding for each neoantigen selected from analysis of a tumour sample from a patient (and there may be any number of such). This insert will be in a fixed mRNA backbone: such elements will be the only variant will be in each mRNA insert. Where lipid nanoparticles are also used, the elements making up the nanoparticles will be consistent across products, meaning its constituents will not be altered; however, there is scope for there to be minor variations in relative proportions of these constituents when suitably justified and supported by the relevant CMC pharmaceutical development/validation data. Beyond these changes, where either the mRNA backbone or the nanoparticle element is changed, this will be considered a new product and testing to support that new product will be expected as if it were the initial product. This backbone will be supported by testing into the elements described below. Once established, this dataset can support use of product with mRNA insert(s) selected by analysis of the patient's tumour.

Initial testing should prove the principle that the mRNA construct produces a specific immune response which should have an anti-tumour effect. As many experimental options are available, the MHRA is not prescriptive in this aspect: developers should satisfy themselves as to the potential benefit to the patient to be treated, in the knowledge that the MHRA will review the evidence base that supports that conclusion. However, the mode of action should consider that many target antigens will be intracellular: the product should be shown to induce a relevant immune response. Testing should explore the distribution of administered mRNA and components of the lipid nanoparticle, including duration of exposure to, and metabolic fate of, elements of the lipid nanoparticle. It is acceptable to cross-refer to studies with other mRNA constructs, if these are shown to be relevant. Where a product intended for clinical use is notably different from that used in prior non-clinical studies, bridging studies may be useful to support the expectation that the revised product will retain efficacy and have a similar safety profile. Testing is also expected to explore safety of the administered product in a manner resembling the intended clinical use, taking account, where relevant, of ICH and WHO guidance documents noted above.

This stage seeks to characterise the potential activity and safety of this use of mRNA and the drug delivery system (e.g. lipid nanoparticles). Subsequently, there should be a record of use of the specific product used in a specific patient that should consider why the product was expected to be of use to treat the patient.

939 Data from the first stage of testing should be supplied in applications for a clinical trial
940 authorisation and for a marketing authorisation. For the second stage of testing, these data
941 should be retained for inspections and could be used in later submissions.

6. Clinical aspects

6.1. Introduction

Developers of individualised mRNA cancer immunotherapies should consult the EMA guideline on the evaluation of anticancer products in humans.

We envisage that the evidence of clinical efficacy and safety to support a marketing authorisation application would come from studies of an investigational medical product that is representative of the proposed commercial product from the quality perspective, considering the design and manufacturing aspects covered in the previous sections. It is recognised that the variable part of the mRNA sequence is likely to be unique to each clinical trial participant, and moreover, unique to each patient that receives the immunotherapy post-authorisation. The clinical development of mRNA cancer immunotherapies should include investigation of (not limited to):

- Pharmacodynamic activity including immunogenicity, and potential markers of efficacy and safety
- Optimal dose, frequency, route of administration and treatment duration
- Appropriate oncology setting including treatment line
- Optimal timing from surgical resection to start of treatment
- Need for sequential or concomitant therapy including immunotherapy
- Efficacy using clinically relevant endpoints for chosen setting
- Safety including administration-related reactions (e.g. intramuscular injection or intravenous injection/infusion), reactogenicity, immune-related adverse events, and other off-target effects

6.2. Changes to product design steps

When designing the pivotal clinical trial(s), the product design steps should be fixed for the duration of the trial (see section 3 of the guidance). After completion of the trial, recent or planned changes to the product design steps could reduce the external validity of the clinical trial data and introduce uncertainty into the evaluation of benefits and risks. Therefore, the clinical documentation to support any licensing submission should describe any changes to the product design steps and justify that the efficacy and safety of the commercial product can be inferred from the non-clinical data and clinical trial data.

6.3. Considerations for randomised placebo-controlled trials

As individualised therapies may have some variability in manufacturing time necessitating different administration timing from patient to patient, the administration timing for patients randomised to placebo may also need to be varied to maintain the study blind. To provide a valid comparison the patients in the placebo group should receive treatment in line with standard of care and should not receive sub-optimal treatment because of factors related to the active treatment group. In particular, efforts should be made to ensure that in the placebo arm the time from surgery (or biopsy) to any co-administered treatment is in line with standard of care.

In some cases, a delay to co-administered standard of care treatment is unavoidable in the individualised immunotherapy arm (e.g. the mechanism of action requires certain timing in relation to the individualised immunotherapy). In this scenario the use of sham/placebo treatment in a double-dummy design could facilitate avoiding the delay of standard of care in the placebo arm.

If, to maintain the study blind, it is considered unavoidable to delay the co-administered standard of care treatment in the placebo arm to match the individualised immunotherapy arm, the developer should provide evidence that the treatment comparison remains valid, for example, any superiority of individualised immunotherapy + standard of care vs standard of care alone is generalisable to the real-world setting, where standard of care may be administered sooner; real-world data could be used in support. This should only be considered in exceptional circumstances and strong justification that the delay to standard of care treatment is unavoidable will be required.

The timing of randomisation and choice of analysis populations should be carefully considered to ensure they correspond to the study objectives. Possible study objectives could be to describe the benefit of the strategy of deciding to try and use an individualised immunotherapy, and/or to describe the benefit of using such a therapy once it is available.

Use of the estimands framework as described in the ICH E9(R1) addendum is encouraged to aid these considerations.

7. Post-authorisation aspects

When planning pharmacovigilance systems developers should consult EU guidance on Good pharmacovigilance practices (GVP) as well as MHRA guidance on Exceptions and modifications to the EU guidance on good pharmacovigilance practices that apply to UK MAHs and the MHRA. Developers should also be aware of MHRA Guidance on pharmacovigilance procedures.

The information in the above guidance should be followed for all individualised mRNA cancer immunotherapies. The principles outlined in the EMA Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products also apply. The relevant aspects of GVP P. II guidance, such as immunogenicity, manufacturing variability and traceability should be considered. Where products will be indicated in paediatric populations, GVP P. IV should be considered. The guidance below outlines additional considerations for pharmacovigilance specific to these products which should be considered. Developers should begin considering plans for pharmacovigilance and risk management early in the development process.

Developers will submit a Risk Management Plan (RMP) as part of the Marketing Authorisation Application (MAA) following the format as described in the existing guidance (see above).

Developers should identify safety concerns using the principles outlined in GVP - Module V as they would with any medicinal product. As these products are ATMPs and are complex in nature, other product-specific aspects should be considered when identifying the safety concerns for these products. The Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products, provides an overview of safety concerns which may be relevant for ATMPs, some of which will be relevant for individualised mRNA cancer immunotherapies, such as quality characteristics, storage, and distribution, administration, traceability, unwanted immunogenicity, persistence, and real-world safety and effectiveness. Developers should also consider whether other aspects specific to these therapies give rise to additional safety concerns, taking into consideration the individualised nature of the approach, the neoantigen selection process, the delivery mechanism, and the tumour site and stage for example. Safety concerns such as reactogenicity, immune-related adverse events, infusion related reactions, possible off-target effects, safety in special populations, safety in patients with autoimmune disease and safety in immunocompromised /immunosuppressed patients are also appropriate to consider.

Linking to genomic data when reporting suspected adverse drug reactions as part of routine pharmacovigilance should be considered, as appropriate.

Given the novelty of individualised mRNA cancer immunotherapies, it would be expected that post-authorisation safety studies (PASS) be included in the RMP, to characterise the long-term safety and effectiveness of the products in a real-world clinical setting and to further characterise safety concerns in the RMP.

The safety concerns and study objectives should be considered when selecting a study design for a PASS. GVP - Module VIII discusses study design and data sources. Consideration should be given to whether existing data sources, such as cancer registries like the National Cancer Registration and Analysis Service would appropriately capture data

or could be amended to meet the study objectives or if the set-up of a new data collection system will be needed. The EBMT and the collection of data on CAR T cell therapies is an example of an existing data source being adapted for use in a new product class. It is preferable that the PASS includes a comparator population, for example using real-world data sources. An appropriate comparator will be essential where the benefits of therapy need to be established. As currently it is intended that the therapies will be used in the adjuvant setting, it will be important to try to differentiate the safety profile of these therapies from the safety profile of other treatments patients have received. It will be important to consider how long patients will be followed up for, to ensure that any long-term effects of the therapies are captured. Opportunities to use existing electronic health records with appropriate data linkage to enable long term follow-up should be considered. Patient genomic information may provide insights into determining mechanisms for certain adverse events, such as immune-related events.

An important consideration in the design of a PASS and pharmacovigilance systems in general for individualised mRNA cancer immunotherapies, is examining how changes to the AI/ML which performs the neoantigen selection will impact the safety and effectiveness of the therapy. Developers should put in place systems to record which 'version' of the AI/ML performed the neoantigen selection for each batch of the therapy (to include documentation on the training data sources and other software dependencies). Developers should consider what information would need to be captured and what analysis may need to be performed to monitor differences in the safety and effectiveness profiles of the products with different 'versions' of the AI/ML.

The neoantigens included in the product can be individual to each patient, though it is assumed that some of the same neoantigens or combinations of neoantigens will be present for multiple patients, and some products may not be fully individualised. It is possible that different neoantigens could lead to different adverse effects. As safety signals arise in a post marketing setting developers will need to consider how they will examine if the signal is related to a specific neoantigen.

Traceability will be a key pharmacovigilance requirement for individualised mRNA cancer immunotherapies. As outlined in previous sections of this guidance traceability will be vital at all stages of manufacturing, distribution, administration, and pharmacovigilance. Traceability is essential to ensure the correct patient receives the correct product and to allow for adverse reactions experienced by patients to be linked with the specific product administered. The RMP should include discussion on measures in place to support traceability. It will be essential to ensure linkage between pharmacovigilance systems and traceability data. As part of the traceability aspects, developers should plan how information on the individualised aspect of the product will be available to patients and their treating physicians. As part of risk minimisation, novel methods for communicating and storing this information should be considered (e.g. use of barcoding).

Developers should consult GVP - Module XVI in order to inform the selection of risk minimisation measures. Given the potential for handling and administration errors it seems likely that educational materials for healthcare professionals would be warranted and would help ensure traceability. Control programmes may be warranted, for example product distribution only to accredited healthcare facilities demonstrating the appropriate processes and infrastructure to ensure product traceability. Other additional risk minimisation measures

for individualised mRNA cancer immunotherapies such as educational materials for patients or a patient card will need to be considered for each product using the criteria set out in GVP Module XVI. Methods for evaluating the effectiveness of risk minimisation measures should be discussed in the RMP, informed by GVP - Module XVI Addendum II.

8. Information for patients, healthcare professionals, and the public

Patients, carers, healthcare professionals and the wider public should have early access to good quality information about individualised mRNA cancer immunotherapies. This is important to inform individual benefit risk discussions between patients and their healthcare professional, ensure safe use, and reduce the likelihood of misinformation.

A summary of product characteristics (SPC) and patient information leaflet (PIL), form part of the conditions of any marketing authorisation and these documents will be standardised across the target population. There may be challenges in conveying relevant information on individualised medicines within the current format of these documents. A public assessment report (PAR) including a lay summary would be published within 30 days of granting a marketing authorisation. The marketing authorisation holder should work with the MHRA to ensure that the PAR includes relevant information to assist patients, healthcare professionals, and the public.

In the context of individualised mRNA cancer immunotherapies, relevant information (in addition to routine medicines information) could include:

- A description of the design phase of manufacture
- An explanation of the individualised nature of the product and the relevance of clinical trial data
- Provisions regarding ownership, storage of, and access to genetic data (considering the relevant UK regulations)
- Estimated turnaround time from tumour sampling to administration

The timing for provision of relevant information should also be considered, particularly in relation to the timing of surgical resection or biopsy. For example, a pre-operative benefit risk discussion and early treatment decision may mean a shorter turnaround time from tumour sampling to product administration. However, the patient may need more time to understand the relevant information, ask questions, and come to an informed decision.

As an additional risk minimisation measure to address identified safety concerns in the risk management plan (RMP) it may be appropriate to provide educational materials for healthcare professionals and/or patients (see section 7). Any additional non-promotional materials, including press releases and patient-support materials (outside those mandated in the RMP) would require vetting by the MHRA advertising team.

Appendix: List of abbreviations

AI	Artificial Intelligence
ASMF	Active Substance Master File
ATMP	Advanced Therapy Medicinal Products
BP	British Pharmacopoeia
CHM	Commission on Human Medicines
COVID-19	Coronavirus Disease 2019
CQA	Critical Quality Attributes
DNA	Deoxyribo-Nucleic Acid
EC	European Commission
EMA	European Medical Agency
EQA	External Quality Assessment
EU	European Union
EWG	Expert Working Group
FDA	U.S. Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
GAMP	Good Automated Manufacturing Practice
GATK-VQSR	Genome Analysis Tool Kit-Variant Quality Score Recalibration
GMLP	Good Machine Learning Practice
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice
HMR	Human Medicines Regulations
HTA	Human Tissues Act
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
ISO/IEC	International Organization for Standardization (ISO) and International Electrotechnical Commission (IEC)
IVDR	In Vitro Diagnostic Regulation
LNP	Lipid Nanoparticle
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR	Medical Device Regulation
MHRA	Medicines and Healthcare products Regulatory Agency
MIA	Manufacturer's/ Importation Authorisation
ML	Machine Learning
mRNA	messenger Ribo-Nucleic Acid
PAR	Public Assessment Report
PASS	Post-Authorisation Safety Studies
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
Ph. Eur.	European Pharmacopoeia
QbD	Quality by Design
RMP	Risk Management Plan
RUO	Research Use Only
SaMD	Software as a Medical Device
SPC	Summary of Product Characteristics
WHO	World Health Organisation