Regulatory Requirements for Nanotechnology-Based RNA Vaccines and Therapeutics

A Quick-Start Guide

cpi

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The Intracellular Drug Delivery Centre (IDDC)

The Intracellular Drug Delivery Centre (IDDC) is a Centre of Excellence led by CPI in partnership with Medicines Discovery Catapult and three leading universities: the University of Strathclyde, the University of Liverpool and Imperial College London. Funded by Innovate UK's Transforming Medicines Manufacturing programme, with a grant of £10 million over 3 years, the Centre will provide a single point of entry for drug discovery innovators to access new capabilities in intracellular drug delivery.

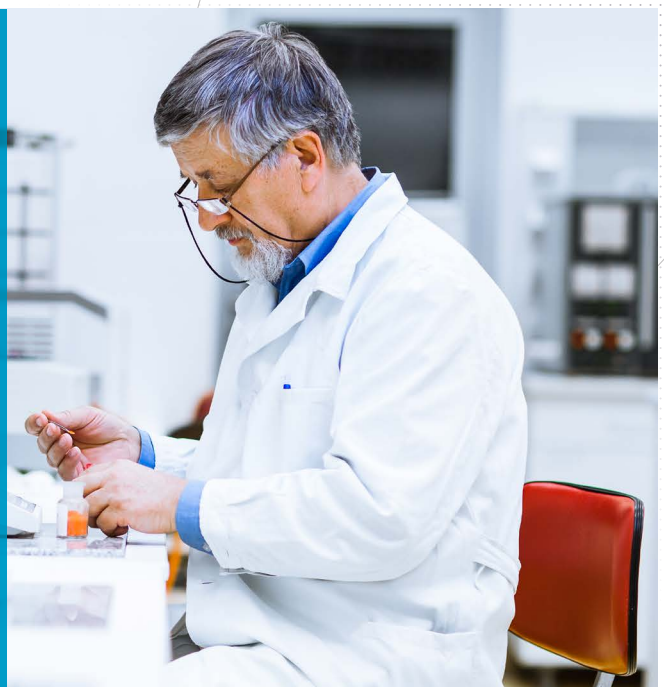
Its focus is to support the development of new drug delivery technologies for RNA payloads and support the progression of promising RNA vaccines and therapeutics towards the clinic.

Find out more here

Regulatory Requirements for Nanotechnology-based RNA Vaccines and Therapeutics

Part of the Intracellular Drug Delivery Centre's (IDDC) mission is to ensure that we are providing those in the ecosystem with the support they need to enable the successful translation of intracellular drug delivery technologies from research to commercialisation, creating the right environment for this sector to anchor and grow in the UK.

Sector engagement has provided clear feedback that those developing new therapies and vaccines with a delivery vehicle were unclear on the regulatory and quality data requirements and the pathways to product registration. The sector would welcome improved guidance or regulatory science support for novel delivery technologies.



The Pathway to Product Registration

Navigating the complex regulatory pathways for nanomedicines can be a significant challenge for innovators and this has been highlighted by the nanomedicine community. The challenges were identified by the Vaccine taskforce mandated LNP and ICD Taskforce, which surveyed UK stakeholders between July 2020 - August 2021, these were confirmed in the surveys carried out as part of the MDC and CPI report "Shaping the UK into an epicentre for complex medicines," and also highlighted in the regulatory session at the NanoMed Europe conference (NME23), which brought together key stakeholders from the European and UK ecosystem in June 2023.

IDDC aims to support innovators progress towards the clinic. Drawing on sector specific expertise within the Medicines & Healthcare products Regulatory Agency (MHRA), we have developed a plan for creating clearer pathways to product registration. In essence, through provision of this guide which includes a decision tree for a "novel" medicinal product, which will help innovators navigate the relevant guidance available, to understand which guidance documents are relevant and how to access support for bespoke interpretation of the guidance.

We have developed this plan for **creating clearer pathways to product registration.**

The Quick Start Guide

Part 1

Regulatory Requirements

The Pathway to Product Registration

Many of the regulatory requirements for RNA vaccines or therapeutics are similar to those for any vaccine or therapeutic; namely

Evidence of efficacy during pre-clinical studies

- Deliver the required beneficial effects for the patient population

Evidence of safety in pre-clinical studies

- The product is safe and well tolerated for the required duration

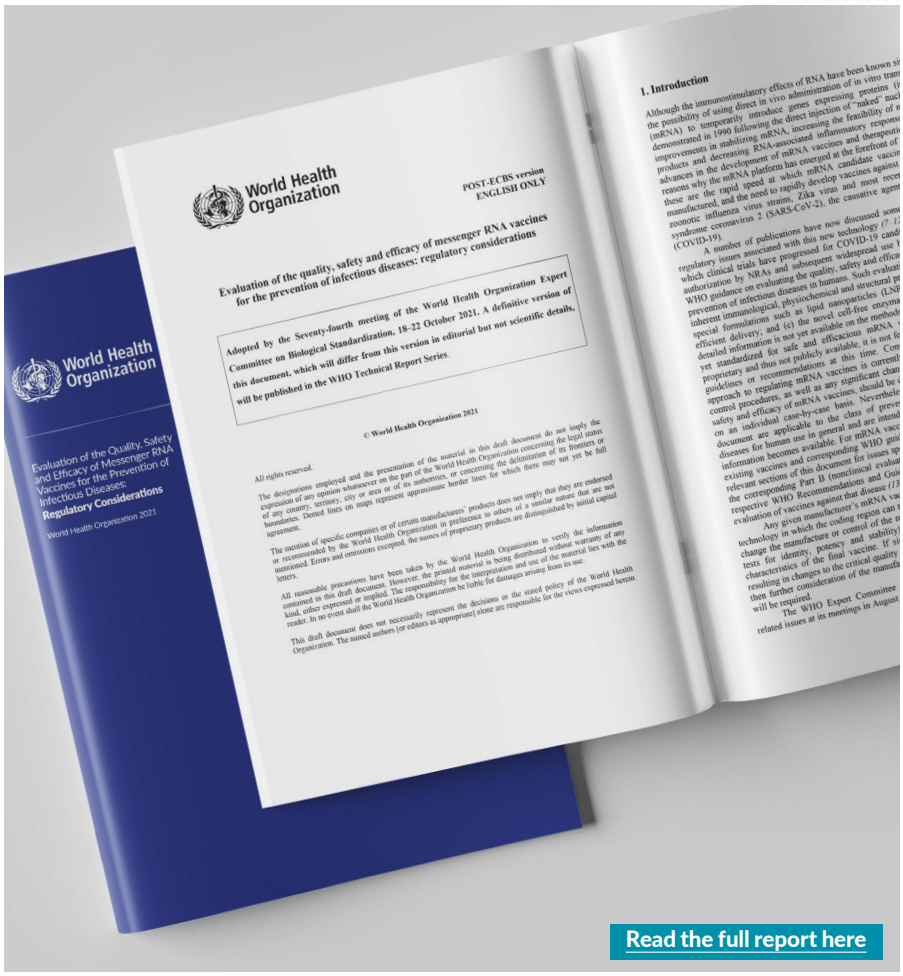
Manufacture

- Quality of the starting materials
- Consistency of manufacture
- Sufficient quantity for human trials

An increase in complex drug modalities over recent years shows that **manufacturing has become the rate-limiting step to product approval** rather than the Phase III Clinical Studies seen in previous years.

Part 2

Defining Regulatory Requirements



International Harmonisation

The International Council for Harmonisation (ICH) provides harmonised guidelines to ensure consistency in drug development globally.

World Health Organization (WHO) documents serve as a benchmark for global acceptability of products and as a basis for defining national regulatory requirements for licensing.

World Health Organization

Evaluation of the quality, safety and efficacy of messenger RNA vaccines for the prevention of infectious diseases: regulatory considerations

Here the WHO defines quality, safety and efficacy required for mRNA vaccines. However, products intended for therapeutic purposes (that is, products for the treatment, mitigation or cure of diseases, including infectious diseases, as opposed to active immunisation for their prevention) are outside the scope of this document.

Part 3

National Regulatory Authorities

To get a drug approved, approach the relevant national regulatory authority in the country or region where the drug is going to be marketed. The process starts with obtaining clinical trial approval and culminates in a marketing authorisation.

Where to go first

Investigational New Drug (IND):

This is generally the first regulatory step, allowing the investigator to conduct clinical trials. Start with the national regulatory body to obtain approval for trials.

We recommend that you start here and then navigate any differences in regulatory guidance as you progress into different territories.

In the UK this is the Medicines and Healthcare products Regulatory Agency (MHRA)'

United States

US Food & Drug Administration
(FDA)
Click here

Europe

European Medicines Agency
(EMA)
Click here

United Kingdom

Medicines & Healthcare products Regulatory Agency

Medicines and Healthcare products Regulatory Agency
(MHRA)
Click here

National Regulatory Authorities: Support & Advice

Seek regulatory advice early in the development programme: Most agencies offer early-stage consultations to guide drug developers through the process.

The MHRA provides advice for innovators with products early in their development phase and for those products that challenge the current regulatory framework.

- MHRA Innovation Office
- Medicines: get scientific advice from MHRA
- Guidance: Innovative Licensing and Access Pathway

Part 4

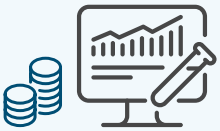
Special Provisions

There are a number of special provisions which have been introduced by regulators to incentivise development in areas which are underserved by current therapies.

To aid progression to the clinic, take advantage of any special provisions which are applicable.

These special regulatory provisions have particular relevance for the development of RNA vaccines and therapeutics:

- **Speed of Development:** Rapid development and agility of RNA-based vaccines and therapeutics can accelerate the response to emerging diseases and medical challenges. Therefore, a corresponding agile regulatory approval process and an opportunity to fast track could be beneficial.
- **RNA can be engineered to address a wide range of diseases,** including genetic disorders, cancer, infectious diseases, and rare diseases; many are considered orphan indications. mRNA vaccines have the potential to be more rapidly tailored to different diseases, or different variants of a disease, by changing the mRNA. They can also be more easily personalised to target the unique profile in each individual patient or for people with rare diseases. Therefore, platform RNA technologies can provide commercially viable opportunities to address rare and orphan indications and this is supported by regulatory authorities who offer certain benefits for drugs with orphan designation going through the regulatory process.
- **Key players in the global RNA vaccines and therapeutics market include large and small pharma with significant innovation driven by the SME sector.** To promote the development of new medicines, regulatory agencies have developed initiatives to support SMEs.



To promote the development of new medicines, **regulatory agencies have developed initiatives to support SMEs**.

Reference:

- 'Demystifying regulatory designations in drug development' by Boyds

Resources:

Orphan Status

- Orphan Drug Development
- Orphan Drug Designation (EU & UK)
- Orphan Medicinal Products
- Orphan Drug Designation in the US, EU & GB

SME Status

- Payment easements and waivers for small and medium companies
- Micro, Small and Medium-sized Enterprise Status in the EU and UK

Fast-Track

- Fast Track, Breakthrough Therapy, Accelerated Approval, Priority Review
- Fast-track your marketing authorisation

Early Access to Medicines Initiatives (EAMS)

- Early Access to Medicines Scheme - Information for Applicants
- Early Access to Medicines Scheme

Part 5

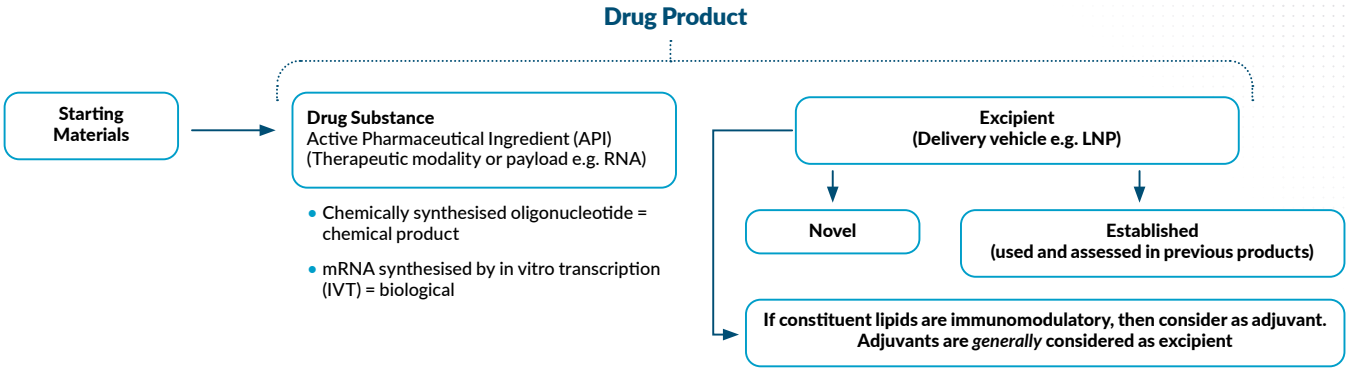
Classification of Products

Medicinal Products for RNA therapeutics fall under several different statuses, such as vaccines, advanced therapy medicinal products (ATMP), simple biological medicinal products or chemical medicinal products.

Regulators classify each component of a new drug based on its use in the product. The therapeutic modality is considered to be the active substance. Starting materials are the various raw materials and intermediates used to make an active substance. Inert substances in drug formulations are considered excipients, and include substances that improve drug delivery but do not otherwise have their own therapeutic effect on the body.

For complex medicines and vaccines, the various materials and substances are subject to different levels of scrutiny requiring different levels of documentation. Therefore, it is important to understand how to classify the components of the drug product and how the requirements for each are described in the guideline documents.

There may be differences in the classification of drug components dependent upon the regulatory authority.



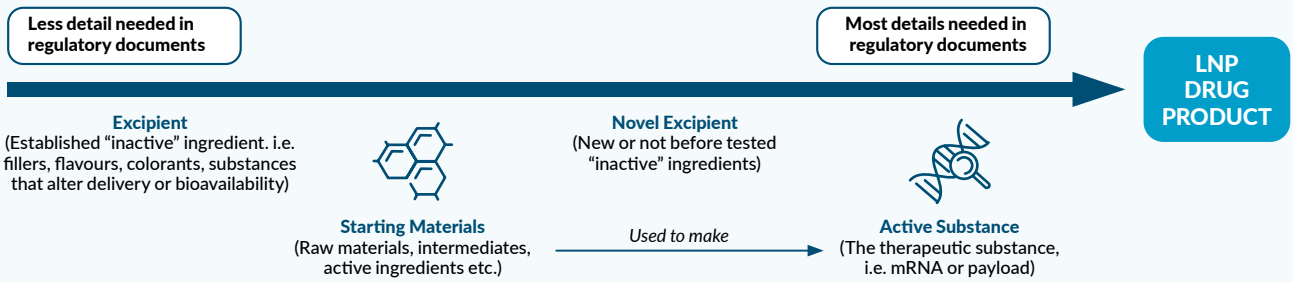
In this figure, classification of the materials used in the drug product are outlined. However, the innovator should consider the function of the drug substance and also the activity, if any, of the excipient. For instance, if it is considered that the ionisable lipids or LNP has pharmacological effect, then follow HMR requirements as follows:

> "Active substance" means any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions.

In this case, there is a requirement for the scientific data to be provided in the dossier which demonstrates the pharmacological, immunological or metabolic action etc.

For instance an "excipient" which has pharmacological activity would also require additional detail on the manufacturing process and the GMP status would be increased. It is therefore important to consider the classification early to ensure that the correct data is provided and the correct level of GMP is applied, to ensure progression to the later stage clinical trials.

RNA-LNPs: Navigating the regulatory challenges – Pharmaceutical Technology

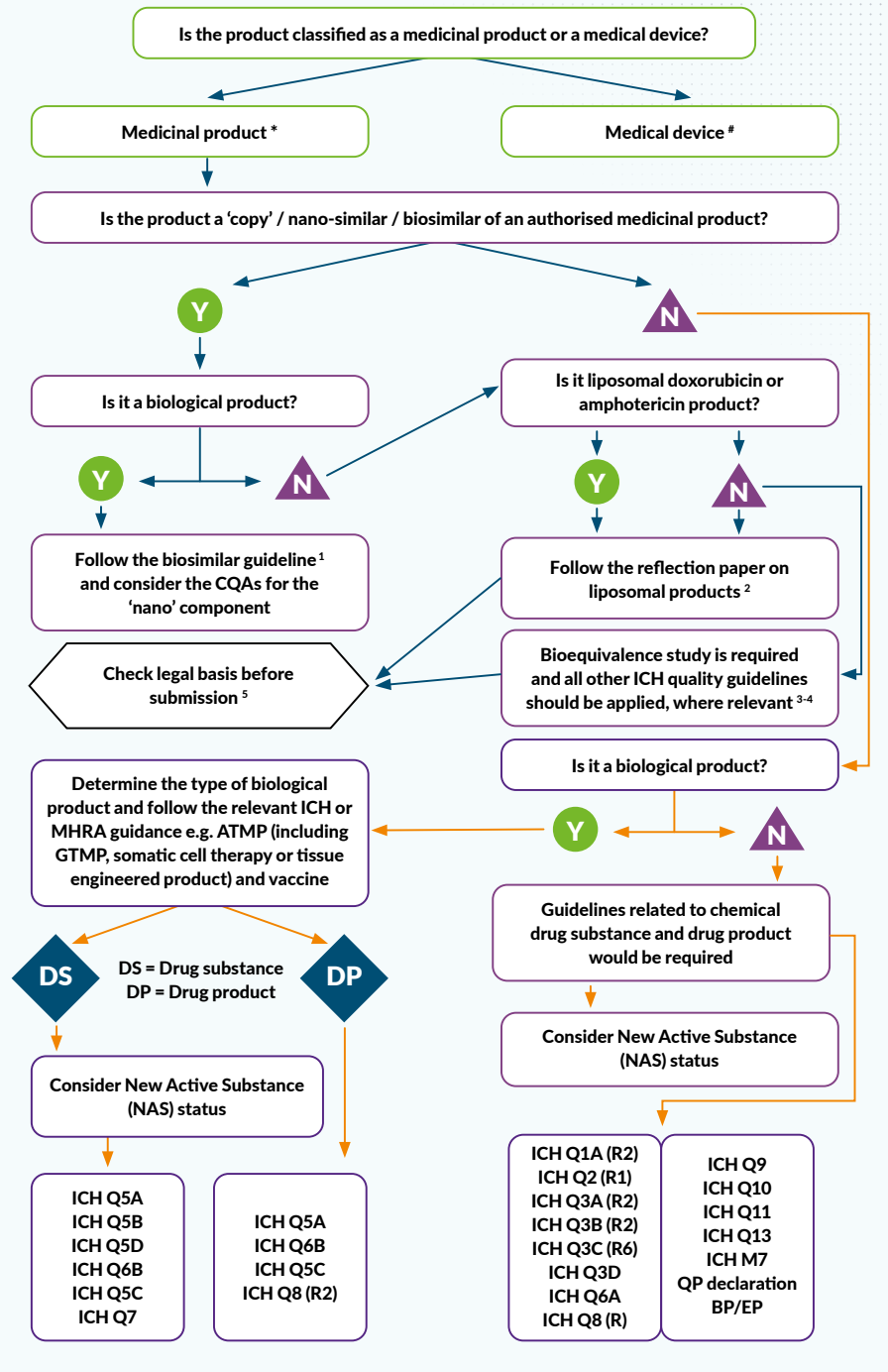


Part 6

Decision tree for navigating nanotechnology-based products

The MHRA have created a decision tree for this guide to help innovators navigate a regulatory pathway for nanotechnology-based products for medical application. It helps innovators define their product and points to the relevant ICH guidance documents.

Decision tree for navigating nanotechnology-based products for medical application



References

* Reference to Human Medicines Regulation 2012 should be made for the definition of a Medicinal Product.

Reference to Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002) should be made for the definition of a Medical Device. Consideration for medical devices is outside the scope of this decision tree.

1. Guidance on the licensing of biosimilar products
2. Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product (EMA/CHMP/806058/2009/Rev. 02)
3. Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **)
4. Comparator products in Bioequivalence/ Therapeutic Equivalence studies
5. Types of application (legal basis)

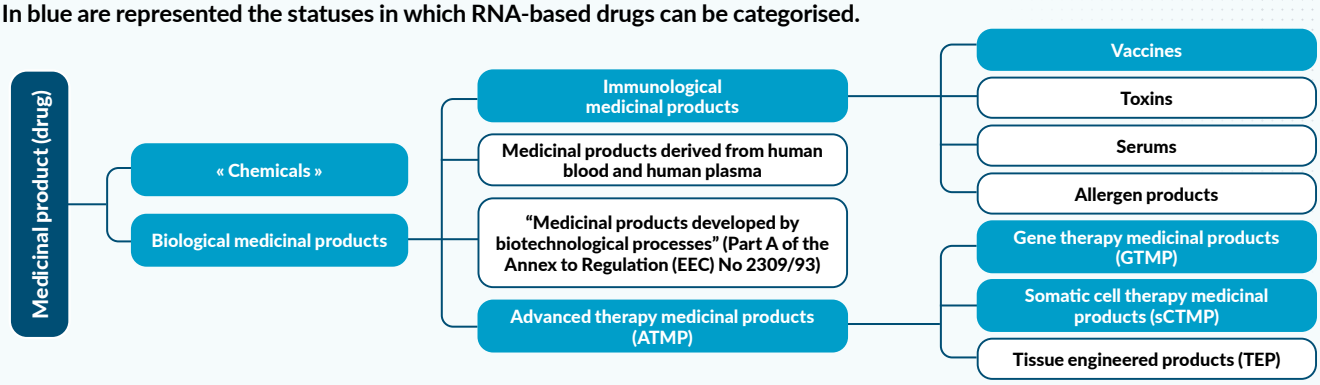
Part 7

Classification of Drug Substance (Active Pharmaceutical Ingredient)

A number of oligonucleotide and RNA-based drugs are in development or approved. These include a diverse collection of mRNAs and non-coding (nc) RNAs such as antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), micro-RNAs (miRNAs), small activating RNAs (saRNAs), RNA aptamers and RNA guides. Currently, these products may be categorised into different regulatory statuses. This classification informs the relevant guidance and the necessary studies to be performed, from preclinical through to clinical trials to meet the requirements for safety and efficacy in patients. Caution is required where similar RNA drugs are covered by different legal statuses and a lack of international harmonisation.

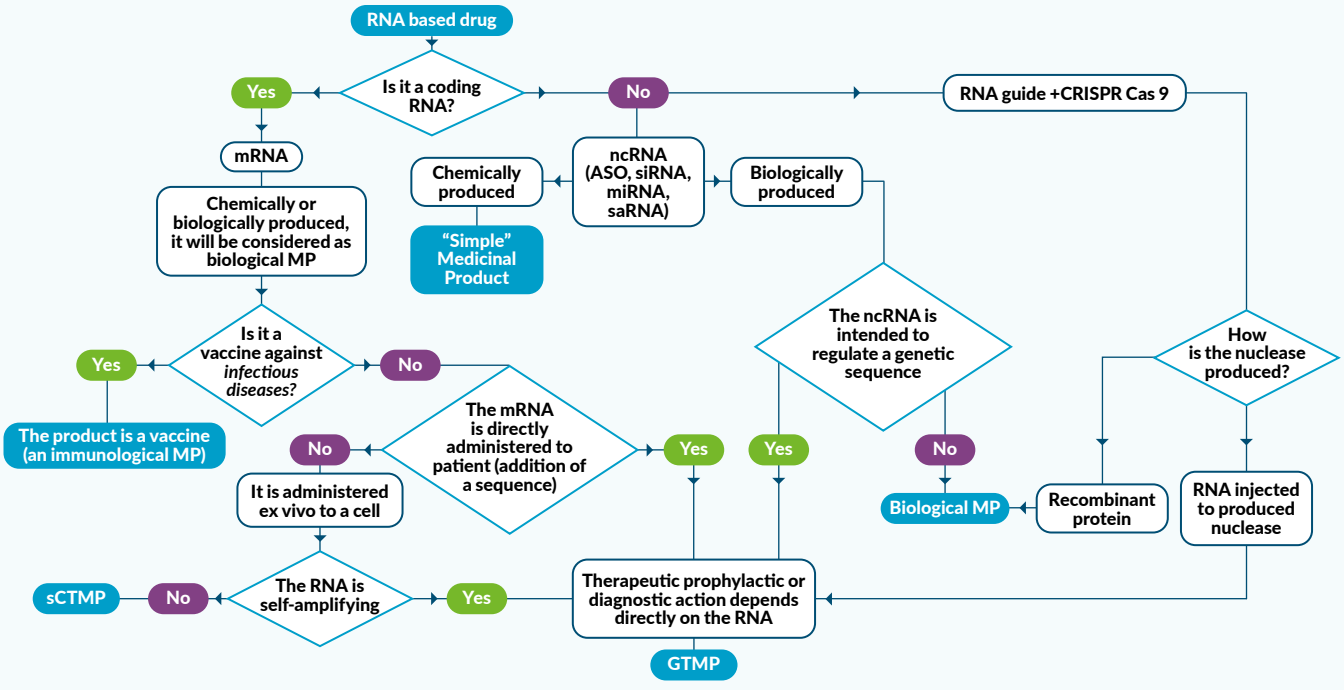
In the article cited below, the authors navigate the classification according to EU regulatory definitions. Investigators should navigate with care and confirm with the local regulatory agency before committing to studies.

Medicinal product statuses according to EU legislation.
In blue are represented the statuses in which RNA-based drugs can be categorised.



Guerriaud M and Kohli E (2022) RNA-based drugs and regulation: Toward a necessary evolution of the definitions issued from the European union legislation. Front. Med. 9:1012497

Proposed flowchart to facilitate the categorisation of RNA-based medicinal products according to the current EU rules.



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