FORUM

Non-clinical aspects of RNA-based drug development

Classification of drugs, impact on non-clinical program, class-specific considerations, examples

Dr Anika Schröter

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About the author

Dr Anika Schröter

Anika Schröter holds a PhD in toxicology and is a registered European Registered Toxicologist. Since 2014 she has been working as a consultant for clients in the pharmaceutical and biotech industry on issues related to non-clinical drug development (e. g. small molecules, biologics, vaccines). Her expertise includes the creation of non-clinical development programs, design and supervision of GLP toxicology studies, or support in consultations with European or non-European authorities. Since 2021 she runs her own consulting company in Vienna.

Non-clinical aspects of RNA-based drug development

RNA-based products are generally divided into a) Coding (mRNA) and b) Non-coding drugs (ASO, RNAi, saRNA etc.).

Product classes are defined by regulatory authorities: 1. Small Molecule, 2. Biological Medicinal Product (a) Advanced Therapy/Cell and Gene Therapy, b) Biotechnology-derived Product), 3. Vaccine. Relevant key guidelines are e.g. ICH M3(R2), ICH S6(R1), WHO guidelines, FDA Guidance for Industry etc.

The following factors influence regulatory classification of RNA-based drugs: a) mode of action, b) manufacturing process/origin, c) indication (and d) regulatory agency)).
An example: Two mRNA products having the same mode of action, differing in the indication are classified in two different product classes.

„Borderline Case Oligonucleotides“: As all non-coding RNAs are currently chemically derived, they are not considered as „biological medicinal products“, consequently they cannot be defined as advanced therapy / gene therapy.
But principles of ICH S6 might be applied for the non-clinical development of oligonucleotides.
The EMA plans on a separate non-clinical guideline on oligonucleotides (until 2024).

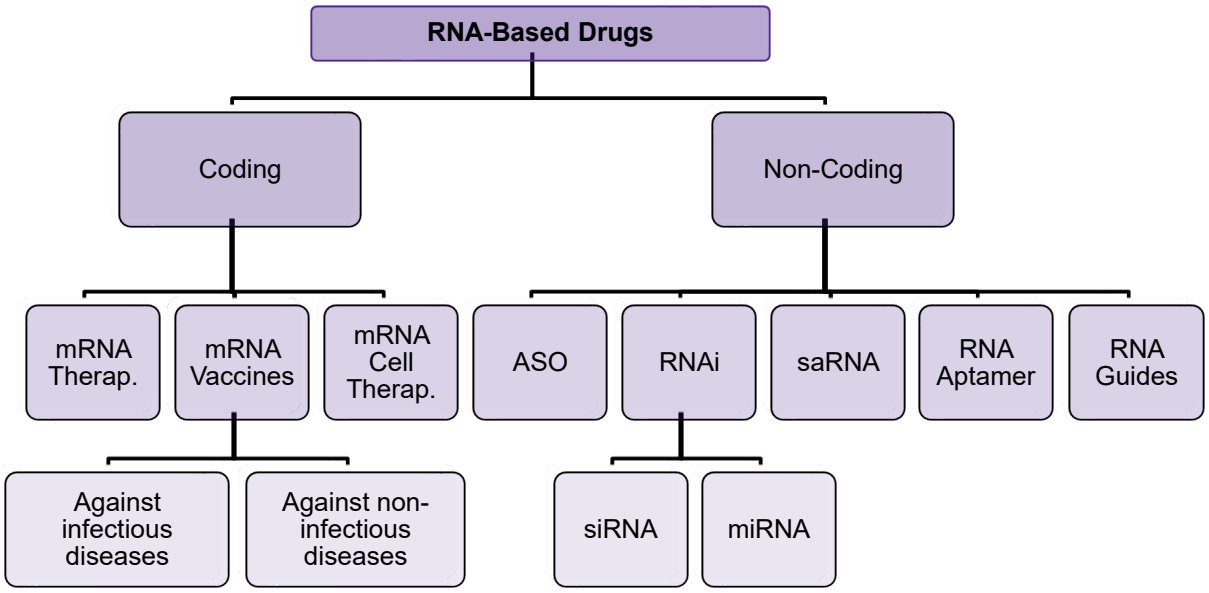
There are different regulatory views of classification of RNA-based products between the EMA and the FDA.
The definition “gene therapy“ (and therefore the harmonization between different regulatory areas) is still under discussion, and an aligned definition is not yet available, except for a description as provided in the newly released ICH S12 guideline.

It is important to define what product one develops, as based on the definition/classification different guidelines apply and thus, a different non-clinical program might be needed.
The three keystones of a NC program for RNA-based products, are, however, comparable to other product types: a) pharmacology, b) pharmacokinetics, c) toxicology. The non-clinical program for different RNA-based products is dependent on the classification.

In summary it can be said, that:

- RNA-based drugs are a highly variable class of products.
- Dependent on indication, mode of action, source (manufacturing) and regulatory region RNA-based products can be classified as small molecule, vaccine, ATMP/GTMP, (biotech drug).
- Classification matters as it significantly influences the required non-clinical program.
- The overall aim of the non-clinical program (i.e. risk/benefit evaluation), is independent from the classification of a product, but the program to get there differs between different product classes.

Variety of RNA-Based Products



Adapted based on Guerriaud&Kohli (2022)

ASO – Antisense Oligonucleotide; mRNA – Messenger RNA; miRNA – Micro RNA; sa – Small Activating; siRNA – Small interfering RNA

Regulatory Classification of RNA-Based Drugs

What kind of drug product classes are defined by Regulatory Authorities and are of relevance for RNA-based drugs?

1. Small Molecule
   - ➢ A medicine, whose active substance is chemically synthesized

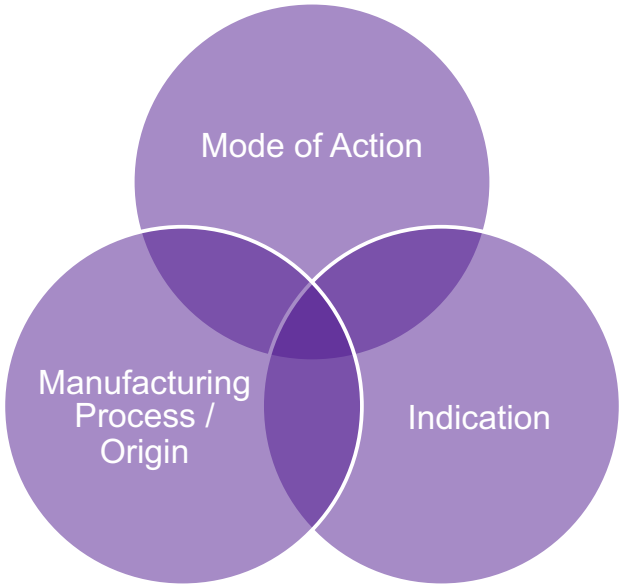
2. Biological Medicinal Product
   - ➢ A medicine, whose active substance is made by a living organism

   a) Advanced Therapy / Cell and Gene Therapy
   - ➢ A medicine, based on genes, cells or tissues

   b) Biotechnology-derived products

3. Vaccine
   - ➢ A medicine, intended to induce specific immunity

What Influences Regulatory Classification?



+ (Regulatory Agency)

Key Objectives of NC Drug Development

Key objective: provide data allowing for a (positive) benefit-risk assessment

- General Principles apply to **all** product types, independent of classification!

How Does the Classification Impact the NC Program?

- Dependent on applicable guideline, the non-clinical program looks different

Small Molecule	**ICH M3(R2)** Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (June 2009)
Biotech-Based Product	**ICH S6(R1)** Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (June 2011)
Vaccine	**WHO** guidelines on Nonclinical Evaluation of Vaccines (2005)
Cell and Gene Therapy	**EMEA/CHMP** Guideline on the Non-Clinical Studies required Before First Clinical use of Gene Therapy Medicinal Products (May 2008) **EMA/CAT** Guideline on Quality, Non-Clinical and Clinical Aspects of Gene Therapy Medicinal Products (March 2018) **FDA** Guidance for Industry – Preclinical Assessment of Investigational Cellular and Gene Therapy Products (Nov 2013)

NC – Non-Clinical

Comparison NC Program for FIH Studies

- Impact of Classification on Timelines and Costs

- **Vaccine**
  - Timeline
  - Costs

- **GTMP**
  - Timeline
  - Costs

- **Small Molecule**
  - Timeline
  - Costs

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