Regulatory and scientific virtual conference on RNA-based medicines

2 February 2023, 09:00 – 16:30 (CET)

Report

The European Medicines Agency (EMA) organised a virtual conference on 2 February 2023 with the aim to promote the development of RNA-based medicines.

This initiative addresses the goal of the EMA Regulatory Science Strategy to 2025 to ”catalyse the integration of science and technology in medicines development”.

The conference focused on emerging RNA technologies beyond vaccines.

The event was open to all stakeholders, registration enabled active participation. The event was broadcasted and recorded, and the video, presentations and biographies of all speakers and their affiliations are available on the EMA website.

The following report captures the content of presentations, discussions, and Question & Answer sessions.

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Welcome and Introduction

Emer Cooke, the Executive Director of EMA welcomed all participant of the workshop highlighting the unprecedented interest in this workshop with more than 1000 registered participants and many more following the broadcast.

Acknowledging the high burden of the COVID-19 pandemic, this workshop will explore some of the opportunities that have arisen from these challenging times. The progress made over the past three years in mRNA and related technologies is unprecedented. We need to ensure the knowledge gained from these advances can now be put into best use for drug development benefitting patients in the future.

This conference will cover a large number of topics and areas of drug development and might not be able to go into in-depth discussions. Relevant areas shall be identified and will be followed-up.

Special thanks to all speakers, chairs and the organising committee for their engagement and commitment supporting a relevant inspiring conference delivering tangible outcomes and relevant follow-up actions.

Steffen Thirstrup, EMA's Chief Medical Officer welcomed and thanked participants for their interest and engagement. With this conference EMA intends to promote innovation based on RNA technology to the benefit of patients. The conference focuses on emerging RNA technologies beyond vaccines.

The objectives of the conference include:

- To identify scientific and regulatory opportunities and challenges of RNA-based innovative medicines.
- To facilitate dialogue between industry/academia and regulators and raise awareness on scientific and regulatory aspects of emerging RNA technologies.
- To identify gaps in regulatory science.

The identification of Regulatory Science gaps is a starting point to explore ways how to address them together with stakeholders. The knowledge gathered from the conference will feed into guidance for upcoming technologies addressing rare diseases, neurological and immune system diseases, cancer – these are critical areas.

Steffen encouraged a lively debate enabling discussions on actions that bring us closer to novel medicines to the benefit of patients.

Session 1: State of the art of RNA technologies

Moderator: Falk Ehmann (EMA)

Sol Ruiz, (AEMPS) provided a summary on the RNA medicinal products approved in the European Union (EU) to date, the regulatory challenges and how regulators can support developers. The regulatory framework is well established for chemicals but also for biologics, including vaccines, allergens, products derived from blood and plasma, and products developed by biotechnological processes such as ATMPs. RNA-based medicines are a new class of molecules for which we gained experience through mRNA-based COVID-19 vaccines. RNA-based medicinal products have been approved and many are under development. There is not yet a consensus on the definition of RNA medicinal products, based on their properties and generation, they can be either a chemical or a biological product. Currently, there are 111 orphan drug designations, 24 paediatric investigation plans and 13 marketing authorization applications of which 10 have been approved by the European Commission (EC) for RNA/antisense oligonucleotide-based medicinal products in EU.

Tal Zaks, (Orbimed) highlighted several challenges related to the development of RNA-based medicines. The first challenge is related to the definition of an RNA medicine: can it be considered a gene therapy? Should the definition be based on the nucleic acid structure or on its mode-of-action? It is important to reach an agreement and to have a clear and open communication with the general public to avoid mistrust since public understanding is necessary to assure the success of new medicines. Another challenge is the pharmacology of RNA-based medicines since their effect is not only mediated by the coding sequence of the nucleic acid but also by the backbone of the molecule which determines the appropriate delivery. In addition, an agreement on the level of evidence needed for RNA medicines authorization is critical and the use of real-world evidence should be leveraged. Finally, the use of RNA platforms could enable important advances such as therapeutic personalized vaccines.

Annemieke Aartsma-Rus, (Leiden University Medical Center) presented an overview on anti-sense oligonucleotides (ASOs) which are chemically synthetized DNA or RNA sequences that target an RNA molecule in a sequence-specific manner. To use these oligonucleotides as medicinal products, they need stabilization and several modifications (backbone and sugar) to assure the correct bioavailability and delivery to the target tissue or organ. ASOs have two main effects: they can either knockdown a toxic protein (gain-of-function or a key protein in a pathological pathway) or restore the synthesis of a missing protein via splicing modulation. Currently, there are three approved ASOs for the knockdown of proteins (mipomersen, inotersen and volanesorsen) and they act by activating RNAase H that will cleave the ASO/target RNA hybrid. On the other hand, ASOs that restore a missing protein act by favoring the inclusion of an exon or exclusion of an intron in the final RNA product. This splicing modulation works on cryptic splicing mutations that cause the inclusion of a part of an intron (part of a gene transcript that does not code for protein) resulting in the premature arrest of protein synthesis. Currently, nusinersen is approved in the EU and in the US for the treatment of spinal muscular atrophy and the FDA approved four additional ASOs for the treatment of Duchenne muscular dystrophy that can restore dystrophin. Annemieke also listed several safety considerations on the use of ASOs such as an exaggerated pharmacology (excessive knockdown) or off-target effects like the downregulation of the target protein in a tissue where the expression is not pathological (especially when the drug is delivered systemically). Eventually, she underscored the importance of engaging with regulators in the early phase of drug development and presented the case of milasen, a splice-modulating ASO developed for a personalized treatment of a child with an orphan disease within only one year from the initial diagnosis. This case inspired academic researchers worldwide to develop personalized ASOs (n-of-1 treatment).

Questions and Answers

What area of RNA technologies has the greatest potential?

The delivery of mRNA using novel classes, especially to reach certain tissues, e.g. brain and lung.

For Antisense Oligonucleotides (ASOs), the potential is dictated by the tissue where efficient delivery can be achieved. Currently this is the liver after systemic delivery (with GalNac conjugates), the central nervous system after intrathecal delivery and the eye after intra-ocular delivery.

RNA molecules developed in oncology and personalized medicines as well as genome editing have great potential.

What are technological advances that enabled the use, ie delivery and tools targeting mRNAs and ASO medicines?

For ASOs, the discovery of phosphorothioate allowed the improvement of bioavailability. Furthermore, advances in manufacturing and scaling up the production was crucial.

The cost of nucleotide sequencing has decreased dramatically and allowed advances in research and development. Scientific collaboration has increased. Moreover, the sharing of data and early access to data during the COVID-19 pandemic e.g. via preprint, has enabled a major boost in research.

What can be learnt from failures of RNA drug developments?

We need to publish also negative results to share the knowledge. It is crucial to include proper controls in pre-clinical (and clinical) studies.

In less than one year, Moderna was able to change adapt a vaccine and deliver it back to the clinic. The translatability of pre-clinical models to the clinical field is essential.

Guidance is needed, especially on quality and non-clinical data. The regulatory system is becoming more transparent, and we need to learn from negative experiences.

Can the RNA platform knowledge be translated to other fields?

The definition of *platform* is important, e.g. when it covers all mRNA and RNA targeting therapies it may be too large. However, within a specific modality, e.g. splice modulation with the same route of administration and the same chemical modification more should be possible. However, it is early days and we have limited medicines approved for each modality, so it is very early for platform approaches for RNA medicines as yet.

Regulators are becoming a source of collaboration, knowledge sharing and enablers, especially on safety risks and adverse events.

Platforms are still not well defined, also for antibodies and other classes of medicinal products.

Individual cancer vaccines: how can we address safety and efficacy without excessive costs?

The development of innovative technologies has improved the accessibility of new medicines and with a scale-up, the costs can go down. For quality, it is quite clear now which are the necessary attributes. Thanks to bioinformatic software, now it is also possible to predict the RNA binding and predict possible off-target effects as well as the benefits. It is important to study the right population that could benefit from a treatment.

What would you change in the current healthcare system?

The public distrust is still present despite the success of mRNA vaccines for Covid-19.

For rare diseases there are many collaborations at every level, but the access and reimbursement is done differently in each country resulting in lot of inequity.

Increasing the dialogue with regulators would benefit the system.

Session 2: Chemistry, Manufacturing and Controls aspects of RNA technologies:

Moderator: Brian Dooley (EMA)

René Thuermer, (BfArM) presented the EU regulator's view on the current CMC regulatory landscape for mRNA-based therapeutics, including its challenges. For oligonucleotide MAAs, major fields where typically a lot of questions are raised are control of starting materials, manufacturing process and control of drug substance and drug product, including analytical methods and method validation.

René then presented the ongoing work to establish an EMA guideline on the development and manufacture of synthetic oligonucleotides. The future guideline will cover antisense and other single strand products, double strand products such as siRNA, and aptamers. In Sep 2022 a concept paper was published, followed by a 3-months public consultation period. From the consultation, 61 comments were received from 7 stakeholders, with the main comments in the themes: purity control strategy, specifications and analytical methodology, comparability and clinical development, and starting materials. Regulatory trends/expectations observed in recent scientific advice applications were described.

For mRNA therapeutics, significant regulatory quality knowledge has been gained from the COVID-19 mRNA vaccine applications. Quality considerations for therapeutics and vaccines are similar, and platform approaches are likely possible. The number of Scientific Advice procedures for a diverse type of mRNA-products is steadily increasing, with main recurring questions on Process Performance Qualification strategies, potency testing, analytical methods and comparability. First PRIME designations were granted.

The EMA's Biologics Working Party (BWP) Workplan for 2023 includes a proposal for a draft EMA guideline on quality of mRNA vaccines with anticipated applicability of some aspects to non-vaccine mRNA therapeutics. A concept paper on this topic for public consultation is expected by mid-2023. Guidance from other regions / organisations e.g. WHO, US Pharmacopeia, will be taken into consideration. The mRNAVAC Working Party has recently been established by the European Directorate for the Quality of Medicines (EDQM), with a first meeting in February 2023.

Daniel Capaldi, (Ionis) presented the industry perspective on synthetic oligonucleotides, on behalf of the European Pharma Oligonucleotide Consortium (EPOC). He presented the industry's views on: oligonucleotide starting materials, terminal sterilisation of oligonucleotides, and impurities in drug substances and drug products.

Regarding starting materials, EPOC recommends applying as much of ICHQ11 as possible: select starting materials with defined and stable structures, with characteristic chemical and physical properties, and provide complete proof of structure and characterization. Impurities need to be characterized, and fates of impurities studied. Distinction between reactive and unreactive impurities may be useful. Starting material specifications should focus on testing critical quality attributes (CQAs).

Another focus of the presentation was product-related impurities, i.e., oligonucleotide impurities derived from impurities in starting materials and reagents, formed due to side- or incomplete reactions of the manufacturing process, or arising by degradation. Complete separation of impurities is likely not practical for most oligonucleotides, and therefore it will be necessary to report impurities as groups or classes. It is suggested to do this per structural class since all members of such class are subject to the same mechanism of formation and reported results will reflect the success of a particular synthetic step or control strategy. He then presented some key considerations to set the reporting and identification thresholds for impurities. Industry proposes a reporting threshold of 0.20% and an identification threshold of 1.0%.

Finally, Daniel presented industry's view on the EMA guidance on terminal sterilization (TS), more specifically its application to oligonucleotides. Industry concludes that for aqueous products, moist heat sterilization methods should be assessed per the decision tree; irradiation or chemical methods not recommended, that feasibility studies should be carried out using the most heat-stable formulation(s) available and container closure of representative materials of construction. Various scenarios where TS is not recommended were described. EPOC plan to publish a paper on this topic in the near future.

Pawel Widomski, (BioNTech) presented the industry perspective on mRNA technology. First, he presented the mRNA technology outlook, a broad mRNA toolkit built out of deep immunological expertise, consisting of multiple mRNA formats, each optimized for specific applications. He then explained the main molecular characteristics of mRNA, and the differences to oligonucleotides.

Secondly Pawel presented industry considerations on group/mRNA platform concepts based on mRNA format in combination with formulation, and, in addition, with aspects common to all groups/mRNA platforms, thus the whole class of mRNA-based therapeutics and vaccines. The concept of mRNA platform was then explained using 'Cancer vaccines' as an example of such mRNA platform, corresponding to an mRNA sequence space for the specific mRNA format, with a corresponding process space. Based on the above, and to enable faster development of new candidates within one platform, a concept for process validation was proposed. Similarly, a stability concept for one platform was proposed. It is proposed to leverage the shelf life of new mRNA products from available platform data using the same formulation, complemented by confirmatory stability studies.

Finally, Pawel presented industry views on applicability of potency assays to mRNA products. Biological activity of mRNA products is a complex function of final drug product properties, including delivery to target cells with suitable delivery system and translation of the mRNA-encoded protein(s). The challenges on potency testing of mRNA products were illustrated, and the problem statement explained: what is the relevant part of the Mode of Action of mRNA-based products that has to be shown for 1) release and stability testing and 2) characterization?

Questions and Answers with Speakers of Session 2, plus additional panel members Lubomir Nechev (Alnylam), Andres Kuhn (BioNTech) and Marcel Hoefnagel (MEB).

Are there any other key topics that are a challenge in oligonucleotide industry in addition to those presented, and how would you like regulators to address them?

One additional topic of interest is the possibility for solution API, and its classification: is it classified as API, or as preformulated intermediate? Skipping the lyophilization step would speed up availability for a large number of patients.

Could you comment from regulatory point of view on whether theoretical risk assessments are sufficient to justify that certain oligonucleotides cannot support terminal sterilisation (TS)?

It is clear that aptamers and conjugates to biologicals and siRNAs do not support TS. Some single stranded ASOs will survive TS conditions, for these a justification must be provided if sterilised in other ways. Not only purity, also particles and appearance should be considered. Risk-based approaches are certainly acceptable for certain classes of oligonucleotides.

Reporting threshold of 0.20% and identification threshold of 1.0% were suggested for oligonucleotides. Could you comment on this?

These thresholds have indeed been accepted for several applications. Views might change depending on evolving analytical technology. Many scientific advice applications have been received where a RT of 0.10% was proposed. Some future discussions are needed.

The EPOC paper is a compromise. What is important is the ID threshold, as this is the limit on unspecified impurities in the API. The limit is driven by quality expectations. That is, when everything works perfectly, there is the expectation that unspecified impurities in the API can be controlled to the identification threshold. Consider, for example, a new reactive impurity in a starting material that leads to an unspecified impurity in the API. If you have the new impurity, it in all starting materials it will be challenging to control the API impurity to better than about 1.0% (because of the multiplicity issue and because you can only analyse your starting materials with a certain degree of accuracy and sensitivity). And all other things being equal, the longer the oligonucleotide, the more difficult it will be to control the resulting impurity in the final API.

The overall control strategy will depend on how far you can go for the starting materials.

Does the 1.0% ID threshold also apply to complex APIs having a GalNac tail?

The ID threshold controls unspecified new impurities. Would it be practical to have separate ID threshold for oligonucleotide impurities that are modified on the oligonucleotide and GalNAc parts? If it's a new impurity, how would we know the location of the modification? The 1 mg amount discussed in Graham et ali is quite important. Sticking to 1.0% is probably the way to go. There is only so much you can do. This topic is driven mainly by quality expectations, rather than by safety concerns. Good characterisation of GalNac constructs is important.

Criticality assessment should be in place for GalNac impurities as well.

What are specific challenges for multivalent vs monovalent mRNA products?

For multivalent products, a combination of ID and ratio testing is needed. Also, potency testing is challenging for multivalent vaccines, as Pawel eluded.

Scientifically speaking it is fair to say that if in characterisation studies you can show that the antigen(s) encoded by the mRNA are correctly expressed in a cell-based assay, then you can use in routine a matrix of functional analytical (physicochemical and immunological) assays as a surrogate for potency.

mRNA is much simpler than a protein (the latter creates the expectation of having a potency assay). For mRNA, all depends on sequence. And if you can show during development that the sequence is translated into a protein, this should be sufficient.

With regard to prior knowledge and platform there is probably more experience in oligonucleotides than in mRNA products?

For oligonucleotides it is reasonable to use platform approaches. As Regulators we have been contacted by a number of companies who asked if generic validation can be applied for method validation. Also, in view of stability approaches, for example antisense oligonucleotides are known to be very stable. Situation might be different for lipid nanoparticles. Regulators are open to discuss proposed platform approaches with companies. The question is how to define the boundaries of the platform, and how to document it? Hundreds of pages in the submission are not a good idea.

Regulators have less experience with platform approaches in mRNA technology, but are certainly open to platform and prior knowledge, if it is well justified. It is acceptable to use it as part of the stability strategy and process validation strategy.

If there are new lipids in LNPs; do they need to be developed as NCEs?

They are considered as novel excipients.

When will the draft guideline on oligonucleotides be ready?

There are 2 guidelines the EMA is working on, we decided to start with the synthetic peptides; the oligonucleotides guideline is targeted for end of 2023, beginning of 2024.

Which further papers can be expected from EPOC? And which of the published papers has the biggest impact?

Papers on TS, on comparability and changes in manufacturing process, on higher order structure and aggregation, on platform data, on stability and on microbial control strategy are in the pipeline.

These papers present the current thinking in industry. These are helpful, an excellent initiative, even if from regulator side we might not agree with proposed thinking/approaches. The goal is to have an ongoing dialogue between regulators and industry.

Session 3: Non-Clinical aspects of RNA technologies:

Moderator: Brigitte Anliker (PEI)

Haiyan Zhou (University College London, UCL) presented opportunities for the non-clinical development of RNA-based medicines including the use of advanced genomic technologies for the identification of new therapeutic targets, the development of new chemistries, modes of action and delivery systems. New pre-clinical models, e.g. 2D models and 3D organoids derived from human somatic cells are relevant because genetic diseases are human-specific. The importance of collaboration between academia and industry was highlighted.

Challenges for the non-clinical development of RNA-based medicines opportunities include identification and mitigation of on- and off-target toxicity and tissue- or cell-targeted delivery. Up to 40% of the RNA-based therapeutics accumulate in the kidney and 40-50% in the liver after systemic infusion, leading to the requirement of tissue or cell-targeted delivery.

The identification and use of animal models and in vivo testing to study human-specific medicines as well as the difficulty developing personalized RNA-based medicines due to the low number of patients is a relevant challenge. Clear guidance on evidence requirements for approval of new medicines is needed.

Susan Goody (Moderna) presented opportunities to streamline the development of RNA-based therapeutics with the definition and adoption of a platform approach enabling an increased development and availability of treatments by building confidence in medicines using same platform. A faster public health reply with streamlined regulatory review would also be more cost effective and reduce animal use.

To leverage non-clinical platform data, elements of the platform that can be leveraged and elements integral to the drug composition, e.g. delivery vehicles or RNA sequence elements need to be defined.

Leveraged platform data that may be relevant for each drug, i.e. non clinical safety, pharmacokinetics or biodistribution data needs to be identified.

The confidence in the scientific rational for leveraging data, i.e. reproducibility and consistency of platform data, knowledge of on-target toxicity, data conducted to support similar clinical plans also needs to be defined.

Camilla Svensson (MPA) started explaining the importance of generating pre-clinical data (e.g. to obtain information on pharmacological activity, pharmacokinetics and toxicity). Sometimes, however, information can be used from already available data, when well justified. She then showed the currently available non-clinical guidance. Camilla then explained the opportunities and challenges associated with the development of RNA-based therapy. In terms of opportunity, it should be possible to leverage existing knowledge to optimise nonclinical programs in line with the 3Rs principles. Challenges can be overcome and include the followings: defining a platform, defining requirements for individual products, understand the new vehicles/ligands for delivery as they are very heterogenous among stakeholders, availability of a pharmacologically relevant species. We have also a shortage of non-human primates and we should use them only when absolutely necessary. Camilla then listed the key points that still need to be addressed in non-clinical safety evaluation: on-target toxicity, off target toxicity and chemistry-dependent class effects, the safety of the formulation/conjugation, the immunogenicity/reactogenicity and the pharmacokinetics, Finally, she strongly encouraged developers to interact at an early stage.

Questions and Answers

How extensive should platform data be?

It is difficult to answer as it depends on different parameters. For instance, whether this is for *in vitro* studies or an *in vivo* studies, where there is more variability. It is also difficult to know how many *in vivo* studies you need for each product because it depends on how much we know already on a specific compound.

Experience from platforms should be analysed and used when established new designs.

If one platform parameter changes, e.g. the size of the nanoparticle (NP), how to proceed? Do you need to start with studying the size of the NP?

Depending on how much knowledge already exists and what size range of NP are considered. Quality data also needs to be taken into consideration to obtain the safety profile of the size of NP.

Do you agree that in vitro models can replace animal models? What about the safety assessments?

Animal models have been crucial to assess drug safety. Before replacing animal use, there is the possibility to reduce the number of animals used by platform approaches and/or cellular models derived from human cells to support human studies.

Models should be validated and demonstrate capability to test the safety profile. Qualification advice[ii] was recommended to have the model accepted by regulators.

Are there structural mRNA motifs to facilitate specific organ-specific translation e.g. in the brain, bone marrow?

There should be elements that can be integrated to allow the translation in certain tissues. Single-cell RNA sequencing may support the finding of such elements.

Will animal models not necessarily be needed for certain developments?

There are many cases, e.g. oncology vaccines, without appropriate animal model to demonstrate safety. Every model has limitations and adaptation according to disease/drug is necessary.

The EMA acknowledges certain developments of specific products without relevant animal model.

Session 4: Clinical aspects of RNA technologies

Moderator: Ralf Herold (EMA)

The session on clinical aspects sought to primarily address past, present, and future challenges with RNA therapeutics in clinical research, such as translation into clinical trials, dose-finding, iterating between clinic and laboratory, toxicity and long-term safety.

David Henshall, (Royal College of Surgeons, IE) addressed the academic perspective elaborating on research and progress in the area of epilepsy and making the case of RNA therapeutics for brain diseases. Current epilepsy therapies do not treat the underlying pathophysiology; new treatments are needed for epilepsies with monogenic causes and acquired epilepsy such as after brain injury. RNA medicines can likely be used for loss and gain of function mutations in the case of monogenic epilepsies but also for pathologies underlying acquired epilepsies.

- Working together with patients, David reported that RNA-based personalized treatments are sought by patients, who may avoid frequent/daily dosing and burdensome side effects, but that patients are

concerned about the possibility to abrogate ("switch off") effects of such medicines and deliver routes (e.g. intrathecal/spinal injection).

- Challenges are the limitation of translocation via the blood brain barrier, the optimal chemistry for best tolerated and effective RNA molecules, the prediction of off target effects and interactions between RNA medicines and standard treatments.
- Translational opportunities include that brain tissue is available from patients suffering from seizures after surgery and can be maintained viable for testing RNA medicines. Trials of administering RNA and gene therapies could be conducted with patients in advance of a planned epilepsy surgery where the resected tissue could be studied for treatment effects (e.g. molecular, electrophysiological, morphological and biochemical findings). Circulating RNA can be used as biomarker for patient selection ("companion diagnostic") and for pharmacokinetic/pharmacodynamic studies of RNA medicines. In addition, dogs from certain breeds suffer from drug-resistant epilepsy and may need to be euthanized, so this is a potential model with a known natural disease course for pre-human trial testing or even developing a veterinary medicine.
- The future holds plausible avenues for developing RNA medicines that respond only to active pathologies such abnormal cells involved in seizures, engineering on- and off-switches for RNA medicines and gene therapy, developing 'network' medicines by targeting microRNA with ASOs, and the development of cell-directed targeting of RNA medicines.

Michael Wenger, (BioNTech) addressed clinical research challenges from an industry perspective including experience from the area of oncology and immunology.

- With respect to RNA cancer immunotherapeutic medicines, the two prominent approaches are using mRNA to produce an "off the shelf" set of fixed antigens in a cancer patient, and the individualized approach where mRNAs encoding for currently up to twenty neo-antigens relevant for a patient's malignant tumour (such as determined by biopsy or resection) are prepared and administered.
- Challenges with mRNA-based medicines are in particular the concept of a platform, for example for extrapolating non-clinical and clinical safety data across candidates generated within the platform, broader leveraging of post-authorisation data of mRNA vaccines for other conditions, and dose-finding in clinical trials given there is little correlation between RNA amount and protein translation, and between immunogenicity and tumour-shrinking effects. In addition, despite the available evidence, there still seem to be limited understanding from same stakeholders of the lack of genome integration potential of RNA, consistent understanding of the non-integration of RNA into the genome is still limited, 'learning' algorithms for selecting neo-antigens are challenging, and as a matter of principle, immunotherapy including by means of RNA medicines may work best when the tumour burden is low for which validated biomarkers are sought.
- For the future it is expected that the mRNA technology is also used for producing antibodies and cytokines in patients.

Joop van Gerven, Central Committee on Research Involving Human Subjects (CCMO), NL, elaborated on the perspective of an ethics and clinical trials' national competent authority on clinical research of RNA therapeutics. The CCMO evaluated applications for authorisation of more than one hundred clinical trials with RNA therapeutics, with ASOs and siRNAs the most frequent but also including splicing modifiers, coding mRNA and other types. Around 8% of the proposed trials were not authorised because the evidence was deemed insufficient for anticipating a favourable risk/benefit balance for subjects in the trial.

- In the Netherlands, clinical research on RNA-based therapeutics is clearly increasing. A large majority of trial applications were from commercial sponsors and not from academia. Most trials of siRNAs primarily targeted the liver. Clinical uses varied much in trials of antisense RNA medicines.
- Based on their experience, authorisation of clinical trials of RNA-based medicines is facilitated through seeking scientific advice in particular also by academic/non-commercial sponsors, a strong pharmacological rationale including pharmacokinetics and tissue penetration, developing a biomarker for dose-selection in the early development, in early trials with the paediatric population not only pharmacokinetics and safety but also markers of clinical activity/efficacy.

Discussion, Questions and Answers

During the brief discussion, the presenters considered the actors and way of working in clinical research (e.g. collaboration, funding, platform trials, patient engagement, public private partnerships, logistics, statistical methods), and shared their views on what could the most important element to be improved for advancing RNA therapeutics.

The platform/"backbone" approach to RNA therapeutics is held to be broadly safe and thus as opportunity to accelerate the development. However, coordination between developers and users of platform as well as regulators is crucial. There is engagement in public private partnerships but possibly not enough. However, researchers struggle to conduct clinical trials rapidly, and here regulators can help to propel innovation. In addition, questions about the cost of RNA medicines and how use them best from a healthcare perspective need to be discussed, and more flexibility was recommended for determining the value of RNA therapeutics. With respect to supporting academic developers but also for considering RNA medicines not only for rare but also frequent diseases, a wide multistakeholder discussion is needed.

Session 5: Panel discussion

Moderators: Marjon Pasmooij (MEB) and Steffen Thirstrup (EMA)

Arjon Van Hengel, (DG Research and Innovation EC) highlighted that data sharing is fundamental as well as research on unmet medical needs. He presented several European initiatives where RNA technology research could get funding, including collaborative research on health (cluster 1 of Horizon Europe) and the European Innovation Council (delivery of RNA therapeutics and RNA therapies for rare diseases). Moreover, there are several partnerships between the European Commission and member states for instance in the areas of rare diseases and personalized medicine, as well as a mission on cancer. Public-private partnerships also with the health industry (Innovative Health Initiative, IHI) provides funding for academia and SMEs that work with large pharma and other health industry sectors.

Mariette Driessens, Patient Alliance for Rare Diseases (VSOP), underscored the importance of education for patients and the general public. It is also important to implement these new RNA technologies for rare diseases, in particular for paediatric patients. There is an Innovative Medicines Initiative (IMI) project to improve the trials for paediatric patients. Need for good governance and best practices on data sharing.

Jeske Smink, (Silence Therapeutics GmbH) an SME working on siRNA. As SME, additional regulatory guidance and alignment between different member states and between regions is welcomed. For example, guidelines on grouping of impurities. Guidelines should be flexible to accommodate continuous developments and focus on how to do things rather than to set absolute limits. Moreover, they should be appropriate for individual RNA modalities. There are many opportunities for discussions among the different stakeholders to find alignments.

Questions and Answers

How can consortia and patient organisations get in contact with regulators and what can regulators do for them?

In the Netherlands, for gene therapies there is a platform for patient organisations to share information and to contact policy makers. Webinars and meetings are regularly organised. Members of patient organisations are also part of the scientific advisory boards in the Dutch Center for RNA therapeutics (DCRT).

Patients are crucial in the dialogue with developers. Education is multilateral. DCRT reached out to the EMA Innovation Task Force (ITF) even before having a lead medicinal product identified. Subsequent meetings followed with specific products both via ITF and formal EMA-Scientific Advice (SA) within the European 1 Mutation 1 Medicine (1M1M) network. The challenge for academia is the lack of expertise in regulatory affairs but ITF is approachable even with minimal expertise in regulatory science.

Lack of experience in writing regulatory dossiers for individualized therapy (e.g. mutation-based products) and challenges can be overcome only with patients' participation that could allow adaptation of clinical trials to suit their needs.

Could Q&A documents be a quick solution to the lack of guidance/guidelines (which would require more time to be completed)?

Q&A documents would be very useful in early developments and would already provide some guidance specific and appropriate for RNA modalities.

It is difficult to decide when an official guidance is needed, a Q&A is a more flexible option. Stakeholders are welcome to make proposals and challenge the regulators via either EMA's Innovation Task Force (ITF) or Scientific Advice (SA) with justifications/knowledge from literature/experience to trigger discussions.

Regulators are willing to support and to draft guidance when of value. As an example, the EMA Quality Innovation Group (QIG) welcomes proposals on areas that would benefit from guidance from developers with the aim of drafting Q&A documents in collaboration with the Quality Working Party (QWP) and Biologics Working Party (BWP) at EMA.

For platform approaches, when are products considered similar?

Criteria need to be established not only on the company side but also on the regulatory side. Each company needs to provide evidence to show that the platform provides similar products.

More experience and better understanding of the use of RNA molecules in different indications and with different mode of action needs to be gained. In regulatory dossiers, part of the data obtained through a platform approach could be used for dedicated areas e.g. quality.

Some platforms are proprietary approaches (company-specific), but others are similar and share the modality of action and should not be company-specific. It is important to have criteria to define *platforms* and *similar products*. The need for discussion and clarification of proprietary rights and patient-protected platforms that are not broadly shared was highlighted.

Every company is trying to develop their own platform. It is useful to have consistency and harmonization so that platforms are set up in a similar way to allow comparisons of data/products.

The public voice and patients are critical, and the language is crucial to deliver benefits/risks and acceptability of methods/products.

COVID-19 allowed the genetic sequencing of patients in routine care after giving consent: the public needs to be adequately informed to increase participation in trials and sequencing studies. Public understanding is a critical enabler of innovations in this area.

Privacy law is quite strict in the European Union, especially for genetic data. Is this a limitation?

Education can improve participation and for rare diseases, given the unmet needs, people and patients are more willing to participate in research and trials, including genome sequencing studies.

Which pre-competitive areas are funded via the Innovative Health Initiative (IHI)?

Research topics can be proposed via the IHI website. Whereas IHI supports precompetitive research and innovation, projects in a competitive area can be funded via different European funding initiatives under the Horizon Europe programme.

Platform technologies can increase innovations in different broader areas e.g. rare diseases and thereby generate more impact. It is crucial to engage with regulators early, ensuring the evidence collected with these technologies during R&D is valid for decision making.

The level of understanding of RNA technologies is different across EU members states, how do we ensure a common approach to clinical trials?

There is currently little sharing of clinical trial information of RNA-based medicines among members states.

What is the main point necessary to move forward with RNA-based medicines?

Common core data elements for outcomes to advance clinical trials.

Early communication among different stakeholders, including patients and regulatory alignment together with flexibility.

Closing remarks

Sol Ruiz and Steffen Thirstrup both concluded that it had been a very intense but extremely interesting and fruitful day. RNA based medicine has a great potential in a wide range of conditions – many of them where no therapy is currently available. EMA and its scientific experts from across EU will be moving forward building on the lessons learned from mRNA vaccines against COVID-19 and on the already approved products based on RNA technologies. EMA appreciate the many constructive comments received during the sessions and debates of the day. We will take note of these when moving forward developing future guidance and Q&A documents. We will also continue to encourage developers across the board to engage and challenge us either via the Innovation Task Force or via Scientific Advice. EMA will also continue its dialogue with other stakeholders such as patients, caregivers, healthcare professionals as well as developers in industry and academia.

The chairs concluded by thanking the organisers, the speakers, and panelists as well as the close to 1.000 online participants for making the conference happen and for their engagement.

[i] Calculating qualified non-mutagenic impurity levels: Harmonization of approaches Regulatory Toxicology and Pharmacology 126 (2021) 105023 https://doi.org/10.1016/j.yrtph.2021.105023

[ii] https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0