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Report of the European Medicines Agency Conference on RNA-Based Medicines

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RNA-based medicines have potential to treat a large variety of diseases, and research in the field is very dynamic. Proactively, The European Medicines Agency (EMA) organized a virtual conference on February 2, 2023 to promote the development of RNA-based medicines. The 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 RNA technologies (excluding RNA vaccines) and involved different stakeholders, including representatives from academia, industry, regulatory authorities, and patient organizations. The conference comprised presentations and discussion sessions conducted by panels of subject matter experts. In this meeting report, we summarize the presentations and recap the main themes of the panel discussions.

Keywords: RNA-based medicines, regulatory challenges, drug development, European Medicines Agency (EMA), oligonucleotides

Welcome and Introduction

Emer Cooke, Executive Director of the European Medicines Agency (EMA), welcomed all participants to the workshop. Emer highlighted the high level of interest in the workshop, which registered >1,000 participants and many more following the broadcast.

Acknowledging the high burden of the COVID-19 pandemic, the workshop explored some of the opportunities that have arisen in these challenging times. The progress made for the past 3 years in mRNA and related technologies is unprecedented, and it will be important to ensure that the knowledge gained is put to best use in drug development.

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The event was recorded, and the video, presentations, and biographies of all speakers and their affiliations are available on the EMA website: Regulatory and scientific virtual conference on RNA-based medicines.

Steffen Thirstrup, Chief Medical Officer at the EMA, outlined that with this conference, EMA intends to promote innovation based on RNA technology to the benefit of patients. The conference focused on emerging RNA technologies beyond vaccines. The objectives of the conference include the following:

1. To identify scientific and regulatory opportunities and challenges of innovative RNA-based medicines;
2. To facilitate dialogue between industry/academia and regulators and raise awareness on scientific and regulatory aspects of RNA technologies;
3. To identify gaps in regulatory science and find ways to address them. The knowledge gathered from the conference will feed into guidance for upcoming technologies addressing critical areas including rare diseases, neurological and immune system diseases, and cancer.

Session 1: State of the Art of RNA Technologies

Sol Ruiz (AEMPS) provided a summary of RNA medicinal products approved in the European Union (EU), the regulatory challenges and how regulators can support developers. The regulatory framework is well established for chemicals and biologics, including vaccines, allergens, products derived from blood and plasma, and products developed by biotechnological processes such as advanced therapy medicinal products. RNA-based medicines are a new class of molecules for which regulators gained experience through mRNA-based COVID-19 vaccines.

Several antisense oligonucleotides (ASOs) and siRNAs have been approved and many more are under development. There is not yet a consensus on the definition of RNA medicinal products from a regulatory standpoint. Based on their properties and production, RNA medicines are either chemical or biological products. Currently, there are 111 orphan drug designations, 24 pediatric investigation plans and 13 marketing authorization applications (MAAs) of which 10 have been approved by the European Commission (EC) for RNA/ASO-based medicinal products in EU.

Tal Zaks (Orbimed) highlighted several challenges related to the development of RNA-based medicines. The first challenge is the relative lack of clarity regarding the definition of RNA medicines, and whether they may be considered a form of 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 to avoid mistrust, since public understanding is necessary to ensure 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 its 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 of ASOs. Unlike mRNAs, which code for a protein, ASOs are chemically synthetized DNA or RNA sequences that target an mRNA molecule in a sequence-selective manner. For use as medicinal products, oligonucleotides need to be chemically modified to ensure sufficient stability, bioavailability, and delivery to the target tissue or organ. ASOs have two main effects: they can either knock down a toxic protein or restore the synthesis of a missing protein, through splicing modulation.

Currently, there are three approved ASOs that knock down proteins (mipomersen, inotersen, and volanesorsen) by binding to the corresponding mRNA and activating RNase H, which cleaves the mRNA strand of the ASO-/target duplex. ASOs that restore a missing protein act by favoring inclusion of an exon or exclusion of an intron in the mature mRNA product. Splicing modulation works on cryptic splicing mutations that cause the inclusion of a part of an intron, that is, the part of a gene transcript that does not code for protein, resulting in the premature arrest of protein synthesis.

Splicing-modulating ASOs include Nusinersen, which is approved in the EU and in the United States for the treatment of spinal muscular atrophy, and four ASOs indicated for the treatment of Duchenne muscular dystrophy, which are approved in the US Annemieke listed several safety considerations regarding the use of ASOs, including considerations of exaggerated pharmacology (excessive knockdown) and off-target effects such as downregulation of the target protein in a tissue where expression is not pathological (especially when the drug is delivered systemically).

Annemieke underscored the importance of engaging with regulators in the early phase of drug development and presented the case of Milasen, a splicing-modulating ASO developed for a personalized treatment of a child with an orphan disease within only 1 year from initial diagnosis. This case inspired academic researchers worldwide to develop personalized ASOs (*n*-of-1 treatment).

Discussion

The speakers stated that areas of RNA technologies with significant future potentials include the delivery of mRNAs using novel therapeutic classes, especially to certain tissues, for example, brain and lung. For ASOs, potential efficacy in a particular tissue is dictated by the extent to which efficient delivery can be achieved. Currently, efficient delivery is restricted to the liver (after systemic administration with GalNac conjugates), the central nervous system (after intrathecal administration) and the eye (after intraocular injection). RNA technologies including genome editing and molecules developed in oncology have the potential to enable personalized medicine.

Discussion of technological advances that enabled the development of ASOs included improvements in manufacturing and scale-up, which were crucial for clinical implementation of ASO and mRNA medicines. From a diagnostic aspect, the cost of nucleotide sequencing has decreased dramatically and improved the identification of patients with rare diseases that can be treated with ASO or mRNA medicines. Scientific collaboration has increased. Moreover, the sharing of data and early access to data during the COVID-19 pandemic, for example, through preprint, enabled a major boost in research.

To learn from failures in mRNA and ASO drug development, negative results need to be published. Especially with ASOs, it is crucial to include proper controls in preclinical studies. The translatability of preclinical models to the clinical field is essential. The benefit of guidance on quality and nonclinical data requirements was highlighted.

The topic of platform development was discussed. A precise definition of *platform* is important and overly broad definitions, for example, those covering all mRNAs and RNA-targeting therapies, would likely be too broad to be useful. Platform definitions based on shared modality, for example, splice modulation, route of administration, and chemical modification are more useful. During the discussion, it was also highlighted that regulators are becoming a source of collaboration, knowledge sharing and enablers, especially on safety risks and adverse events. The new EU pharmaceutical legislation includes articles on *platforms*.

Highly personalized treatments, such as individual cancer vaccines and personalized ASOs or mRNAs might pose a challenge to health care financing. Looking toward the future, the development of innovative technologies has improved accessibility of new medicines, and with increases in scale, it is anticipated that the costs can decrease. Thanks to bioinformatic software, it is also possible to predict the RNA binding and possible off-target effects, thereby improving preclinical development and increasing the chance of designing an efficacious and safe ASO or mRNA therapy.

Asked about the one issue they would like to change, the panelists listed public mistrust of the pharmaceutical industry, which, despite the success of mRNA vaccines for COVID-1, remains disappointingly high. For rare diseases, there are many collaborations at many levels, but access and reimbursement are done differently in each country, resulting in a lot of inequity. Finally, in increasing the dialogue with regulators overall would benefit the system.

Session 2: Chemistry, Manufacturing, and Controls Aspects of RNA Technologies

René Thuermer (BfArM) presented the EU regulator's view on the current chemistry, manufacturing, and controls regulatory landscape for RNA-based therapeutics, including its challenges. For synthetic oligonucleotide MAAs, typical questions focus on 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 for the development of synthetic oligonucleotides.

The guideline will cover antisense and other single-stranded products, double-stranded products such as siRNA, and aptamers. In September 2022, a concept article was published, followed by a 3-month public consultation period. From the consultation, 61 comments were received from 7 stakeholders, with the main comments focused in the areas of purity control strategy, specifications and analytical methodology, comparability and clinical development, and starting materials. Regulatory trends and expectations observed in recent scientific advice (SA) 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 SA procedures for a diverse range of mRNA-products is steadily increasing, with main recurring questions in the areas of Process Performance Qualification strategies, potency testing, analytical methods, and comparability. First PRIME designations were granted for mRNA therapeutics.

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 nonvaccine mRNA therapeutics. A concept article available for public consultation is expected by mid-2023. Guidance from other regions and organizations, for example, WHO and US Pharmacopeia, will be taken into consideration. The mRNAVAC Working Party has recently been established by the European Directorate for the Quality of Medicines, 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). Daniel presented the industry's views on oligonucleotide starting materials, terminal sterilization of oligonucleotides, and impurities in drug substances and drug products.

Regarding starting materials, EPOC recommends applying as much of ICH guideline Q11 as possible. Therefore, starting materials should have defined and stable structures, with characteristic chemical and physical properties. Complete proof of structure and characterization of starting materials should be required. 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.

Another focus of the presentation was product-related impurities, that is, 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, therefore, the reported results will reflect the success of a particular synthetic step or control strategy. Daniel 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 guideline on terminal sterilization [1], and more specifically, its application to oligonucleotides. Industry considers that for aqueous products, moist heat sterilization methods should be assessed and irradiation, or chemical methods are not recommended.

Feasibility studies should be carried out using the most heat-stable formulation(s) available and a container closure of representative materials of construction. Various scenarios where terminal sterilization is not recommended were described. EPOC has recently published an article discussing terminal sterilization of oligonucleotide [2].

Pawel Widomski (BioNTech) presented the industry perspective on mRNA technology. First, he presented the

mRNA technology outlook, a broad mRNA toolkit based on immunological expertise, consisting of multiple mRNA formats, each optimized for a specific application. He then explained the main molecular characteristics of mRNA, and the differences to ASOs.

Pawel presented the concept of mRNA platforms using ''Cancer vaccines'' as an example. The platform corresponds to an mRNA sequence space for a specific mRNA format, with a corresponding process space. Based on the aforementioned, and to enable faster development of new candidates within the platform, a concept for platform process validation was proposed. Similarly, a platform 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's 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 using a suitable delivery system and translation of the mRNA to protein. The challenges of potency testing of mRNA products were illustrated and the possibilities and limitations of analytical methods for release testing discussed. With appropriate justification and sufficient characterization, data waivers would not be excluded but should be discussed with the regulators.

Discussion

Regulatory topics that currently attract high attention in the oligonucleotide industry are the need for terminal sterilization, selection and justification of starting materials, purity control strategy and the concept of solution active pharmaceutical ingredient (API).

The EMA guidance on terminal sterilization is applicable to oligonucleotides. For aqueous products, moist heat sterilization methods should be considered per the decision tree; feasibility studies should be carried out using the most heat-stable formulation(s) available and container closure of representative materials of construction. Aptamers, oligonucleotides conjugated to proteins and siRNAs are not suitable for terminal sterilization.

However, some single-stranded ASOs are more stable and, therefore, justification of sterile filtration and aseptic processing must be provided. The impact of terminal sterilization on assay, degradation products, and other attributes such as particulate matter and appearance should be considered. Risk-based approaches are acceptable for certain classes of oligonucleotides. EPOC published an article on this topic [2].

Regarding the control strategy for impurities, industry suggests a reporting threshold of 0.20% and an identification threshold of 1.0%. The thresholds have been accepted for several approved oligonucleotide therapeutics, although views may change with evolving analytical technology. SA applications have been received where a reporting threshold of 0.10% was proposed. The identification threshold, which determines the limit on unspecified impurities in the APIs driven by quality expectations rather than safety concerns. The quality expectation is that unspecified impurities in the API are controlled to the identification threshold when all aspects of the control strategy perform as expected.

Industry suggests that an identification threshold of 1.0% is about the best that can be done for oligonucleotides. Consider, for example, a new reactive impurity in a starting material that leads to an unspecified impurity in the API. If the new impurity is present 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 of the limitations of the analytical methods used for the starting materials, particularly regarding accuracy and quantification limits. All other factors being equal, the longer the oligonucleotide, the more difficult it will be to control the resulting impurity in the final API.

For oligonucleotides, companies have proposed prior knowledge and platform approaches for analytical method validation and stability. The challenge is how to define the boundaries of the platform and how to document it. Regulators have less experience with platform approaches in mRNA technology but are certainly open to platforms and prior knowledge as part of the stability strategy and process validation strategy, for example, assuming proper justification is provided.

The draft EMA oligonucleotide guideline will consider stakeholder and is targeted to be published for public consultation at the end of 2023, beginning of 2024. EPOC is currently working on articles on comparability, higher order structure and aggregation, platform data, stability, and microbial control strategies. From the regulators' side, the articles are helpful because, even if the proposed approaches is not supported, they trigger dialogue between regulators and industry.

Finally, analytical challenges for multivalent mRNA products were discussed. For these products, a combination of identity and ratio testing is needed. In addition to this, the need for routine potency testing was discussed, that is, if in characterization studies it is demonstrated through a cell-based assay that the antigen(s) encoded by the mRNA (ie, the sequence) are correctly expressed, a matrix of functional analytical (physicochemical and immunological) assays could be justified as a surrogate for potency testing.

A concept article for a draft EMA guideline on the quality of mRNA vaccines is targeted to be published for public consultation by mid-2023.

Session 3: Nonclinical Aspects of RNA Technologies

Haiyan Zhou (University College London, UCL) presented opportunities for the nonclinical 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 preclinical models, for example, 2D cellular 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 nonclinical development of RNA-based medicines opportunities include identification and mitigation of on- and off-target toxicity and tissue- or cell-targeted delivery, which leads to the requirement of tissue or cell-targeted delivery.

The generation and use of suitable animal models and *in vivo* testing to study human-specific medicines, as well as

the difficulty in developing personalized RNA-based medicines due to the low number of patients, are relevant challenges in the preclinical development of RNA-based medicines. Clear guidance on evidence requirements for regulatory approval of this new class of medicines is needed.

Susan Goody (Moderna) presented opportunities to streamline the development of RNA-based therapeutics. She suggested that to leverage nonclinical platform data, a few elements need to be defined across the industry, in partnership with regulatory agencies. These elements include the elements integral to the composition of the drug (eg, RNA sequence elements), the data specific to each drug (eg, nonclinical safety, pharmacokinetics, and biodistribution data) and the confidence in scientific rationale for leveraging nonclinical data.

Adoption of a platform approach has the potential to accelerate drug 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.

A potential decision tree was proposed to help sponsors and regulators align on the scientific rationale that can be used to leverage nonclinical platform data and included inflection points such as answering whether the downstream pharmacodynamic effect of the RNA cargo would be expected to impact nonclinical data outcomes, whether common platform elements are used, and if there is defendable scientific rationale to use platform data.

An example of nonclinical toxicology/safety pharmacology package with and without leveraging studies was presented, showing the efficiencies gained on streamlining drug development. Overall, reduction in nonclinical cycle times, responsible use of animals, and efficiencies gained in regulatory dossier preparation were proposed as benefits to companies for adopting a platform approach.

Camilla Svensson (MPA) started explaining the importance of generating nonclinical data, for example, 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 nonclinical guidance. Camilla further 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 optimize nonclinical programs in line with the 3Rs principles (reducing, refining, and replacing of animals). 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 nonhuman primates and we should use them only when absolutely necessary. Camilla then listed the key points that still need to be addressed in nonclinical 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 with the competent authorities at an early stage.

Discussion

The definition and inclusion criteria of platforms was discussed, for example, whether it is for *in vitro* studies or also *in vivo* studies, and in which case a higher variability can be expected. It is also difficult to know how many *in vivo* studies are required to gain confidence in leveraging a particular study type, because this depends on how much previous knowledge is available on a specific compound. As such this needs to be assessed on a case-by-case basis.

Experience from established platforms should be analyzed and used when new designs are explored. If a platform quality attribute parameter changes, for example, the size of the nanoparticle, the necessity for additional nonclinical analyses depends on how much knowledge already exists, and whether there is confidence that there would be no impact for that change based on scientific data. Quality data also need to be taken into consideration to obtain the safety profile of the size of nanoparticle.

Animal models have been crucial to assess drug safety. Before replacing animal studies, 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 [3] was recommended to have the model accepted by regulators.

There are cases, for example, oncology RNA-based ''therapeutic vaccines'', where appropriate animal model to demonstrate safety may not be available. 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

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) 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 and 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.

David reported that RNA-based personalized treatments are sought by patients, as they may avoid frequent dosing and burdensome side effects. Patients are, however, concerned about the possibility to abrogate (''switch off'') effects of such medicines and about the delivery routes (eg, intrathecal/spinal injection).

From a translational aspect, several challenges exist: the limitation of translocation through the blood–brain barrier, not knowing the optimal chemistry for best tolerated and effective RNA molecules and how to predict 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. RNA and gene therapies could be tested as part of a clinical trial in patients undergoing surgery. The treatment could be given directly into tissue to be removed, and the tissue could then be studied for treatment effects (eg, 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 prehuman trial testing or even developing a veterinary medicine.

The future holds plausible avenues for developing RNA medicines that respond only to active pathologies such as 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 20 neoantigens relevant for a patient's malignant tumor (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 nonclinical and clinical safety data across candidates generated within the platform, broader leveraging of post-authorization 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 tumor-shrinking effects.

In addition, despite the available evidence, there still seems to be limited understanding from some stakeholders of the lack of genome integration potential of RNA, consistent understanding of the nonintegration of RNA into the genome is still limited, ''learning'' algorithms for selecting neoantigens are evolving and challenging to fit in a static regulatory filing, and as a matter of principle, immunotherapy including by means of RNA medicines may work best when the tumor 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) elaborated on the perspective of an ethics and clinical trials' national competent authority on clinical research of RNA therapeutics. The CCMO evaluated applications for authorization of >100 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 did not receive trial approval because the evidence was deemed insufficient for anticipating a favorable 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. Authorization of clinical trials of RNA-based medicines was facilitated by several characteristics. There was a clear advantage of seeking SA also by academic/noncommercial sponsors.

Approvals were also expedited by a strong pharmacological rationale, including pharmacokinetics and tissue penetration, and by the availability or development of a biomarker for dose selection in the early development. Finally, approvals of early trials with the pediatric population were problematic if they only focused on pharmacokinetics and safety and eased if they also aimed at (markers of) clinical activity/efficacy.

Discussion

During the brief discussion, the panelists discussed collaboration, funding, platform trials, patient engagement, public–private partnerships, logistics, and statistical methods related to advance development of RNA medicines.

The platform/backbone approach to RNA therapeutics is considered generally safe and thus an opportunity to accelerate development. However, coordination between developers and users of platforms as well as regulators is crucial.

Researchers struggle to timely conduct clinical trials. Regulators could be the enabler facilitating innovation. The Accelerating Clinical Trials in the EU (ACT EU) initiative aims to develop the EU further as a competitive centre for innovative clinical research. ACT EU seeks to deliver on the clinical trial innovation recommendations of the EMA network strategy [4] and the EC's Pharmaceutical strategy [5] for Europe.

An open debate on the costs of RNA medicines and how to ensure their integration and use in health care systems is necessary to ensure that better treatments and health care solutions will reach the patients. More flexibility and a multistakeholder discussion for determining the value of RNA therapeutics is recommended.

Session 5: Panel Discussion

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 EC 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 small and medium-sized enterprises (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 pediatric patients. There is an Innovative Medicines Initiative project to improve the trials for pediatric patients. Need for good governance and best practices on data sharing.

Jeske Smink (Silence Therapeutics GmbH). As SME working on siRNA, 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.

Discussion

Patient organizations and consortia need to collaborate and interact with regulators in a reciprocal manner [6]. Patients are crucial in the dialogue with developers. Education is multilateral. The Dutch Center for RNA Therapeutics (DCRT), of which Annemieke Aartsma-Rus is one of the cofounders, reached out to the EMA Innovation Task Force (ITF) even before having a lead medicinal product identified. Initially this was challenging, but during productive online meetings with ITF, things could be clarified, and subsequent meetings followed with specific products both through ITF and formal EMA 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 as outlined by the DCRT example.

In the Netherlands, for gene therapies there is a platform for patient organizations to share information and to contact policy makers. Webinars and meetings are regularly organized. Members of patient organizations are also part of the scientific advisory boards in the DCRT. Lack of experience in writing regulatory dossiers for individualized therapy, for example, mutation-based products and challenges can be overcome only with patients' participation that could allow adaptation of clinical trials to suit their needs.

Further guidance for the development of RNA-based medicines is necessary. It is crucial to determine when guidance is beneficial, not to overregulate the market, and challenge innovative thinking. Q&A documents are very useful in early developments and would already provide some guidance specific and appropriate for RNA modalities. Stakeholders are welcome to make proposals and challenge the regulators through either EMA's ITF or SA with justifications/knowledge from literature/experience to trigger discussions. 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 BWP at EMA.

For the establishment of meaningful relevant platform approaches, 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 approach ensures safety and efficacy for 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, for example, 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. 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. 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.

Experts stressed the benefit of common core data elements for outcomes to advance clinical trials developing RNA-based medicines. Early communication among different stakeholders, including patients and regulatory alignment together with flexibility, are prerequisites for successful timely relevant developments. Precompetitive research can be proposed and funded by the IHI. Projects in a competitive area can be funded through different European funding initiatives under the Horizon Europe program.

Closing Remarks

RNA-based medicine has a great potential in a wide range of conditions—many of them where no therapy is currently available. The EMA and its scientific experts from across the 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. During this conference, multiple scientific and regulatory challenges were identified by the different stakeholders such as the lack of expertise in regulatory affairs in academia, gaps in guidance for RNA-based medicines, in particular on the quality aspects, and challenges related to the establishment and acceptability of a platform approach.

EMA appreciate the many constructive comments received during the sessions and debates of the day. Regulators at EMA will take note of these when moving forward developing future guidance and Q&A documents. They will also continue to encourage developers across the board to engage and challenge us either through the ITF or through SA. EMA will also continue its dialogue with other stakeholders such as patients, caregivers, health care professionals, as well as developers in industry and academia.

The conference covered a large number of topics and areas of drug development, and it was not always possible to go into in-depth discussions. Relevant areas were identified for follow-up.

Author Disclosure Statement

A.K. and M.W. are employees of and receive stock from BioNTech SE. D.H. and RCSI University of Medicine and Health Sciences hold a patent for the inhibition of microRNA-134 for the treatment of seizure-related disorders and other neurological injuries (US 9,803,200 B2). J.S. is an employee of and receives stock from Silence Therapeutics

GmbH. T.Z. is an employee of ObriMed and nonexecutive director of Teva. A.A.-R. discloses being employed by LUMC, which has patents on exon skipping technology, some of which has been licensed to BioMarin and subsequently sublicensed to Sarepta. As coinventor of some of these patents, A.A.-R. is entitled to a share of royalties. A.A.-R. further discloses being *ad hoc* consultant for PTC Therapeutics, Sarepta Therapeutics, Regenxbio, Alpha Anomeric, Lilly BioMarin Pharmaceuticals, Inc., Eisai, Entrada, Takeda, Splicesense, Galapagos, and Astra Zeneca.

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