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Regulations and research methods to examine the biodistribution of RNA therapies

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INTRODUCTION

A new era in modern medicine has begun with the success of Moderna's and Pfizer's/BioNTech's messenger RNA (mRNA)-based COVID-19 vaccines. Any therapeutic protein of choice can now be encoded on mRNA, encased in lipid nanoparticles (LNPs), and supported by preclinical data in as little as a few weeks. Within a year, the mRNA COVID-19 vaccines were introduced to the market and tested in clinical trials. The European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) consider the COVID-19 pandemic to be a public health emergency due to the immediate availability of vaccines and the risk of less comprehensive pharmaceutical and clinical data at the time of authorization. As a result, SARS-CoV-2 vaccines were granted emergency use authorization in the United States (US) and conditional marketing authorization in Europe. The average time it takes to develop and approve a new drug is ten years, whereas these approvals take much less time. In addition, a regulatory framework that is somewhat lagging has emerged as a result of the rapid growth of mRNA therapeutics. RNA therapeutics is either not included in the current guidelines, do not apply, or lack widely accepted definitions [1].

DESCRIPTION

The terms "RNA therapeutics" and "small interfering RNA" (siRNA) are used throughout this review. According to the EMA and FDA, prophylactic and therapeutic vaccines against infectious diseases are not currently categorized as "gene therapy medicinal products" or "gene therapy products. However, for many of the points discussed, the guidelines for RNA therapeutics and vaccines are comparable. The relevant distinctions between mRNA vaccines and the guidelines for biodistribution studies of RNA therapeutics are highlighted in this review. In addition, we discuss how in vivo RNA imaging methods can fulfill and/or enhance FDA, EMA, the International Council for Harmonization (ICH), and the International Pharmaceutical Regulators Program (IPRP) regulatory requirements. FDA has issued its own guidance document in response to the COVID-19 pandemic, while EMA uses WHO guidelines for vaccines. As a result, the most recent mRNA vaccine guidelines are contained in this FDA guidance document, which will be further updated following the pandemic. The WHO and possibly other national regulatory agencies, such as the FDA and EMA, are also anticipating the release of brand-new mRNA-

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specific guidelines. Although all biodistribution guidelines are non-binding and typically less stringent than those for, for instance, toxicology studies, applicants should keep in mind that additional, binding national and international laws may apply [2].

The molecular characteristics of the drug's presence, persistence, and clearance in both target and non-target tissues are the focus of preclinical biodistribution studies. They aid in the interpretation of nonclinical pharmacology and toxicology findings and are an essential component of preclinical pharmacokinetic studies. Regulators choose, per product, which preclinical biodistribution studies are necessary to start first-in-human studies. However, RNA therapeutics and mRNA vaccines have distinct default approaches. Biodistribution studies should always be conducted for RNA therapeutics, unless the RNA therapeutic's design or type allows for otherwise. Biodistribution studies should also be carried out, but only for brand-new vector classes and when significant modifications are made to vector backbones, formulations, routes of administration, dose levels, and schedules. In contrast, first-in-human studies in Europe and the United States for mRNA vaccines do not require pharmacokinetic studies, which include biodistribution studies, unless the vaccine uses novel adjuvants, formulations, additives, or routes of administration. Before beginning preclinical studies, producers of RNA therapeutics or mRNA vaccines are strongly encouraged to seek assistance from the relevant regulatory body due to the per-product approach. Furthermore, each product will have its own unique set of design guidelines for the biodistribution study. Lipid nanoparticles (LNP) or polymers, for instance, are common carriers or delivery systems for RNA therapeutics. As a result, the therapeutic RNA construct, the carrier/delivery system, the individual components of the carrier/delivery system, and the combined final product may all require preclinical biodistribution studies. Biodistribution of the produced protein product ought to also be investigated for mRNA-based therapeutics [3].

Sometimes, biodistribution studies can be skipped. For instance, neither the Moderna COVID-19 vaccine nor the Pfizer/BioNTech COVID-19 vaccine's preclinical studies included any biodistribution studies for the final mRNA-LNP formulation. Biodistribution studies using LNP formulations encapsulating a different nucleoside-modified RNA (modRNA) sequence were used instead in these applications. New mRNA vaccines that only alter the modRNA component but use the same carrier and route of administration as either the Pfizer/BioNTech or the Moderna COVID-19 vaccine are also implied by the guidelines to not require any additional biodistribution or pharmacokinetic studies. By referring to the data in the Pfizer/BioNTech and Moderna applications, applicants from other businesses could theoretically avoid having to participate in biodistribution studies. However, in practice, access to the experimental data may be restricted by company policy. Additionally, the COVID-19 vaccine (mRNA) platform technologies can be utilized in new vaccines, as stated in FDA guidelines. Biodistribution studies can be avoided when only the protein coding sequence of the mRNA is altered and sufficient justification is provided for not conducting the study. The same reasoning applies to non-vaccine mRNA therapeutics [4].

In addition to the RNA component, individual preclinical studies must support novel carrier components like the lipids in LNPs. For instance, only the ionizable lipid (ALC-0315) and the polyethylene glycol (PEG)-phospholipid conjugate (ALC-0159) were novel components of the LNP formulation that was used in the Pfizer/BioNTech COVID-19 vaccine. In fact, several products that have already been approved make use of cholesterol and distearoyl phosphatidylcholine (DSPC), which meet the requirements of the European Pharmacopoeia. Onpattro®, an EU-approved siRNA drug administered intravenously at a much higher dose than the intended intramuscular dose of the Pfizer/BioNTech COVID-19 vaccine, was specifically mentioned in the provided justification as being used in the LNP. Additionally, the structurally related dioleoyl phosphatidylcholine (DOPC) is approved by the EU for use in intramuscular products. As a result, the EMA only asked for new research on the novel components (ALC-0315 and ALC-0159) and how they are used together in fully formed mRNA-LNPs.

The preclinical product should as closely as possible reflect the intended clinical product and its applications for RNA therapeutics and mRNA vaccines. Nonetheless, deviations can be legitimate. For instance, adjusting dosages to accommodate various species or employing a distinct RNA molecule in a particular carrier. luciferase-encoding mRNA can be used to monitor the distribution of a novel formulation because changing the coding sequence of the mRNA is unlikely to have a significant impact on the physicochemical properties and distribution of mRNA-LNPs. This justification was given for the Moderna and Pfizer/BioNTech COVID-19 vaccines. At long last, albeit the promoting approval of these mRNA immunizations was restrictive, no extra non-clinical in vivo information (counting biodistribution) was mentioned in the European Public Evaluation Reports, showing that the gave information was adequate to a future full showcasing approval.

Preclinical studies of RNA therapeutics should validate the analytical methods used. mRNA vaccines are likewise subject to this. To detect the target (an RNA product, a carrier component, or an expressed protein) at the molecular level and in the relevant biological matrix, applicants must demonstrate that the used techniques, procedures, equipment, and materials are appropriate. This can be demonstrated by referring to published data or by using your own experimental data. Rules on approval of scientific strategies are accessible from various organizations. Quantification limits, methods for obtaining test samples, and the order in which samples are obtained should all be specified. The latter is essential to avoid, for instance, cross-contamination among samples [5].

CONCLUSION

The quantitative Polymerase Chain Reaction (qPCR) is mentioned in FDA, EMA, ICH, and IPRP guidelines for DNA detection. It is important to keep in mind that the European guidelines use the term "Nucleic Acid Amplification Testing," which refers to a more comprehensive approach that may include alternative approaches like loop-mediated isothermal amplification. Reverse Transcription qPCR (RT-qPCR) for RNA is now included in the EMA, ICH, and IPRP guidelines. In nonclinical biodistribution studies, the ICH also lists methods for monitoring the RNA product or the expressed protein product: digital PCR, flow cytometry, in vitro and in vivo imaging methods, enzyme-linked immunosorbent assay (ELISA), immunohistochemistry (IHC), western blot, in situ hybridization (ISH), and "other evolving technologies."

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