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OLIGONUCLEOTIDE-BASED MEDICINES: THE REGULATORY LANDSCAPE IN THE EU AND THE US

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Riassunto

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Oligonucleotide-based medicinal products (ONMs) are a very heterogeneous class of medicines due to the different mechanism of action, therapeutic indications, API production methods, and formulative features. Four main classes of ONMs can be currently identified based on the nucleic acid structure, length, and molecular target: antisense oligonucleotides (ASOs), small-interfering RNA (siRNAs), aptamers and messenger RNAs (mRNAs). When delivered to the cell cytosol, ONs can influence directly or indirectly the translation of proteins and, therefore, they are contributing to revolutionize the prophylaxis and treatment of many human diseases. In this light, this work aims to analyze the features and discuss challenges of ONMs authorized in EU and US. The regulatory history of authorized ONMs was reviewed starting from regulatory portals. As International Nonproprietary Name, the WHO guidelines provide the suffix *-rsen* for ASOs, *-siran* for small interfering double-stranded RNA, including siRNA and miRNA, *-meran* for mRNA molecules, and the infix *-apt-* for aptamers [1].
Until October 2023, 21 ONMs have been authorized by EMA and/or FDA websites. In the US, ONMs are assessed by the CDER of FDA under section 505 of the FD&C Act (21 USC 355). In the EU, ONMs have been authorized ~~by EMA~~ following a centralized procedure, under provisions of Regulation (EC) 726/2004.. Moreover, the majority of ONMs (67%) are classified as orphan drugs by both EMA and FDA.
Most of them are ASOs (52%), and many of them are authorized for musculo-skeletal disorders. From 1998, 11 ASOs have been examined by both EMA and FDA, but only 3 of them are currently authorized in Europe and 7 in the US. Two products were withdrawn for commercial reasons in the US and/or in the EU. At the moment, one aptamer is authorized only in the US. As far as siRNAs, following the first one (Onpattro®) approved by FDA in 2018, 5 additional products have been authorized in the last years. Finally, mRNAs are available only as COVID-19 vaccines, which were approved at the end of 2020 in both US and EU. From a quality point of view, ONMs are mainly produced by using chemical synthetic processes (e.g., solid phase methods). Only, mRNAs are produced by in vitro transcription (IVT) starting from linear DNA. Regarding the delivery platform, only Onpattro® and mRNA vaccines are formulated with lipid nanoparticles.
The overall results reveal how heterogeneous ONMs are in terms of therapeutic indications, API production methods, and formulative features. Therefore, both EMA and FDA are still facing challenges in providing harmonized regulatory requirements and standards for such novel therapeutic classes, staring from the lack of a regulatory consensus on their classification [2]. A potential conceptual misalignment between the US and EU may emerge from the recent EC proposal of Reform of the EU pharmaceutical legislation, which seems to be aimed at classifying all ONMs as ATMPs [3]. However, due to the heterogenicity and innovative nature of ONMs, grounding the regulatory classification on the nature of the API source may be counterproductive. Otherwise, the benefit/risk balance should be assessed both on their peculiar quality aspects related to the manufacturing process and on their efficacy and safety profiles related to mechanism of action.

**Reference**

1. WHO, https://www.who.int/publications/m/item/who-mhp-hps-inn-2022-2, 2022.
2. Thakur S., et al., Front. Pharmacol. 13, 1006304, 2022.
3. EC, https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en, 2023.

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