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Oligonucleotides: Opportunities, Pipeline and Challenges

At Long Last, Nucleic Acid Therapeutics Are Coming of Age

By Tracy TreDenick, Head of Regulatory and Quality Assurance, BioTechLogic

Although meaningful progress toward the development of oligonucleotide therapeutics began in the 1970s, nearly a half century later, only six oligonucleotide drugs have been approved by the FDA as of November 2017. However, the field is gaining momentum and the clinical benefits of the dozens of oligonucleotide therapeutics currently in various stages of clinical trials are extremely promising.

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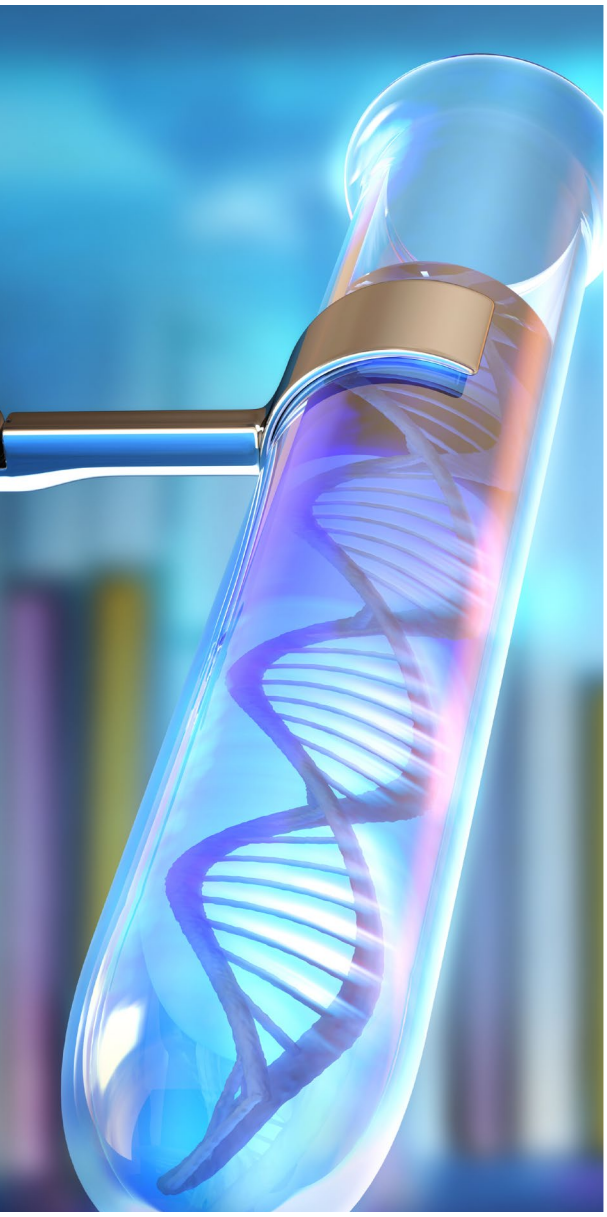
The Promise & Opportunities

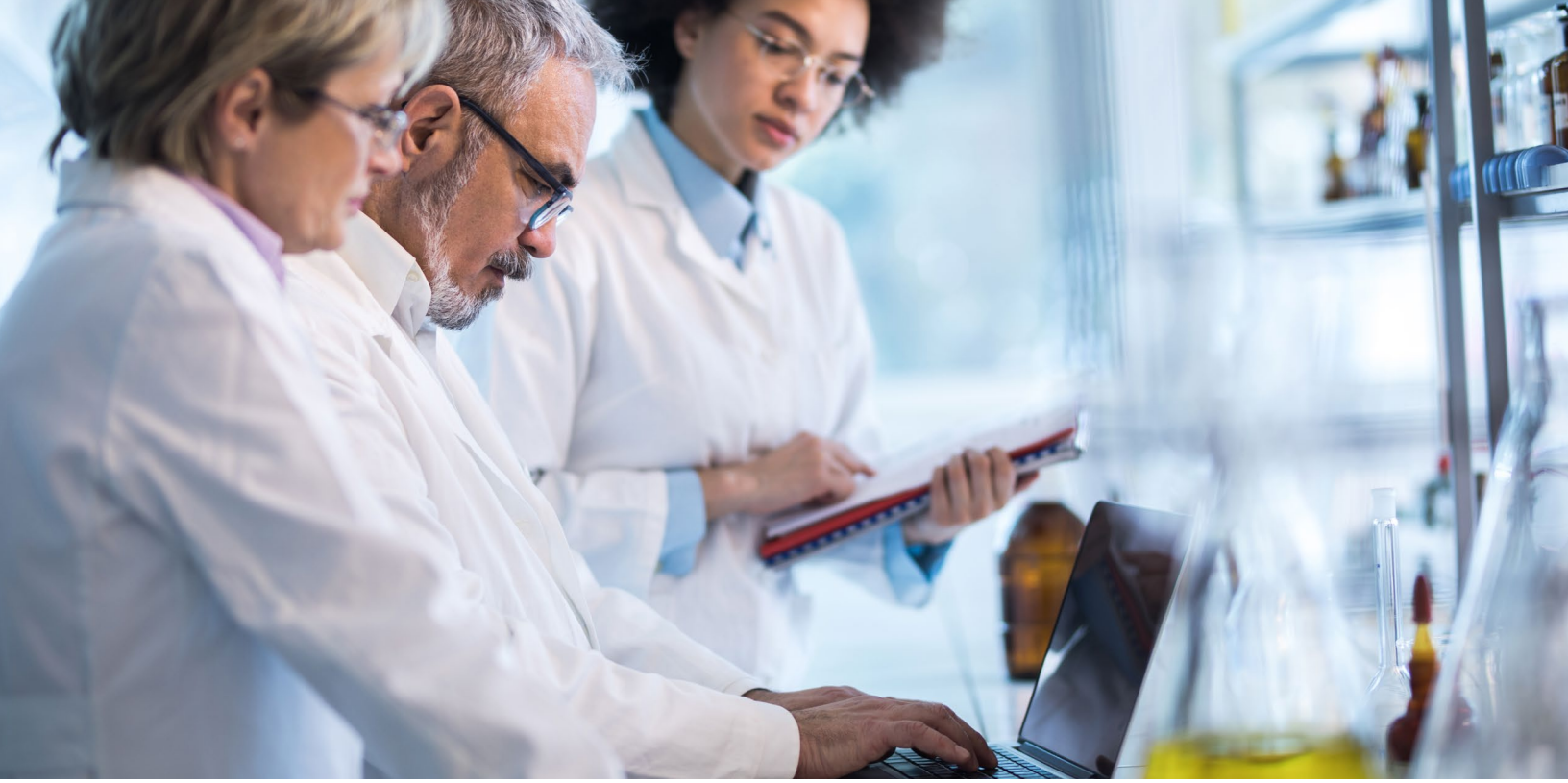
What is so attractive about oligonucleotide therapeutics? Although this class of therapeutics is quite diverse, the excitement and dedication to this work is rooted in the following factors:



- Oligonucleotides offer promising treatment for a wide range of medical conditions.
- They allow for the development of therapeutics that affect protein targets that cannot be effectively treated by small-molecule or protein therapeutics.
- Interfering with RNA function at the cellular level, specific malfunctioning genes can be targeted, manipulated, silenced and/or modulated.
- Immune system modification is possible, offering the possibility of treatment for a multitude of autoimmune disorders that are in many cases extremely challenging to treat with currently available drugs.
- Oligonucleotides are synthesized pieces of chemically modified RNA or DNA. Scaling up for commercial-scale GMP production is more feasible than it is for many cell therapies or other biologic therapies.
- Side effects for many oligonucleotides are more controllable and minimal than the side effects experienced with other classes of drugs.
- As reported by Ryszard Kole in 1993, oligonucleotides can be used to modulate pre-mRNA splicing. Much work has been done to develop therapies targeting Duchenne muscular dystrophy, including progress treating the splicing mutation that causes Duchenne muscular dystrophy. These learnings hold much promise for many other conditions as well.
- In concept, when compared to small-molecular drugs as well as to large-molecule biopharmaceuticals, oligonucleotide pharmaceuticals are much more straightforward to both design and develop.

Given the relatively new commercial viability of the oligonucleotide market, it is difficult to establish a precise value of the market. However, all indications point to a very promising future for viability and future growth. For instance, the oligonucleotide synthesis market is estimated to be $1.92 billion USD by 2020, up from $1.08 billion USD in 2015. Compounding Annual Growth Rate (CAGR) in the oligonucleotide synthesis market is approximately 10.1 percent.

While the market performance of oligonucleotide therapies is still not as predictable as other segments, the future as reflected by both the leaders in the space and the amount of investment and R&D activity, looks very promising. This is not to say, however, that there are not significant challenges to contend with.



The Challenges

While there are numerous challenges the field is currently grappling with, this paper will focus on four: enabling technologies, diversity within this class of therapeutics, delivery challenges and regulatory complexity.

Enabling Technologies

Antisense oligonucleotide (ASO) therapeutics currently represent the most promise and have experienced the most success within the overall oligonucleotide class. As mentioned at the beginning of this paper, it is commonly accepted that the modern age of oligonucleotides and the birth of Antisense Oligonucleotide (ASO) work began in the early 1970s after Nobel laureate Gobind Khorana published his ground-breaking work.

Despite these early days and critical steps in the 1970s, Antisense Oligonucleotide (ASO) therapeutics as a promising set of entities for commercialization began in the early 1990s. However, during this period, there were ongoing supply chain delays, limited synthesis methods which sharply limited the amount of available drug substance, analytical methods were not well developed, and analytical instrumentation technology was often not advanced enough to support the needs of the market.

Advancing analytical methods that better characterize and quantitate both the oligonucleotide of interest as well as any synthesis contaminants have been critically important enabling technologies. For example, new LC/MS methods have been introduced in the last few years that use both low levels of triethylamine (TEA) and hexafluoroisopropanol (HFIP) as a mobile-phase buffer. For reversed-phase (RP) separations, this approach has facilitated reasonable mass spectroscopy (MS) sensitivity. Given that HPLC methods alone are inadequate, this has been one of numerous important analytical advancements as the resolution and richness of characterization that mass spectroscopy (MS) offers is needed.

In addition to analytical method limitations, it was expensive and difficult to produce chemically modified oligonucleotides; therefore, only very small quantities were generally produced causing supply chain problems and shortage of product to work with. However, market leaders have dedicated significant resources toward improving manufacturing efficiency and capacity.

“By developing several proprietary chemical processes to scale up our manufacturing capabilities, we have greatly reduced the cost of producing oligonucleotide drugs. For example, we have significantly reduced the cost of raw materials through improved yield efficiency, while at the same time increasing our capacity to make the drugs. Through both our internal research and development programs and collaborations with outside vendors, we may achieve even greater efficiency and further cost reductions,” commented Stanley T. Crooke, M.D., Ph.D., Chairman, Chief Executive Officer and President, Ionis Pharmaceuticals (then Isis Pharmaceuticals) in its 2014 annual report.

Diversity within Oligonucleotide Class of Therapeutics

Nucleic acid molecules are charged and larger than traditional small molecules, so productive uptake into target organs and cells is often challenging—this is a huge factor in the success of a drug candidate. Given this, careful consideration needs to be given to the size of the nucleic acid drug and the range of chemical modifications that are allowable and still support the mechanism of drug action.

The types of nucleic acid drugs vary in structure (single or double-stranded), in molecular weight (from 2,400-16,000), molecular size/number of nucleotides and number of negative charges. These variances result in a wide variety of mechanics of action as the drug molecules interact with target mRNAs, cells and tissues.

For instance, only limited chemical modifications can be made to small-interfering RNAs while still allowing the necessary proteins in the cell to recognize the molecule. On the other hand, Antisense Oligonucleotides allow for much greater freedom in chemical modification, but the cellular RNase H activity requirements impose restrictions on where sugar modifications can be introduced in the molecules, limiting them to their outer flanks (constructs known as gapmers).

Given both the wide diversity of molecular characteristics and diversity in mechanisms of action, it is impossible to meaningfully lump this class of therapeutics together in broader categories that would facilitate simplified consideration at the regulatory level for instance.

Drug Delivery & Toxicology Challenges

Despite advances at the clinical level, effective delivery of oligonucleotides in vivo continues to be challenging, specifically delivering the active oligonucleotide to correct sites within target cells of target tissues.

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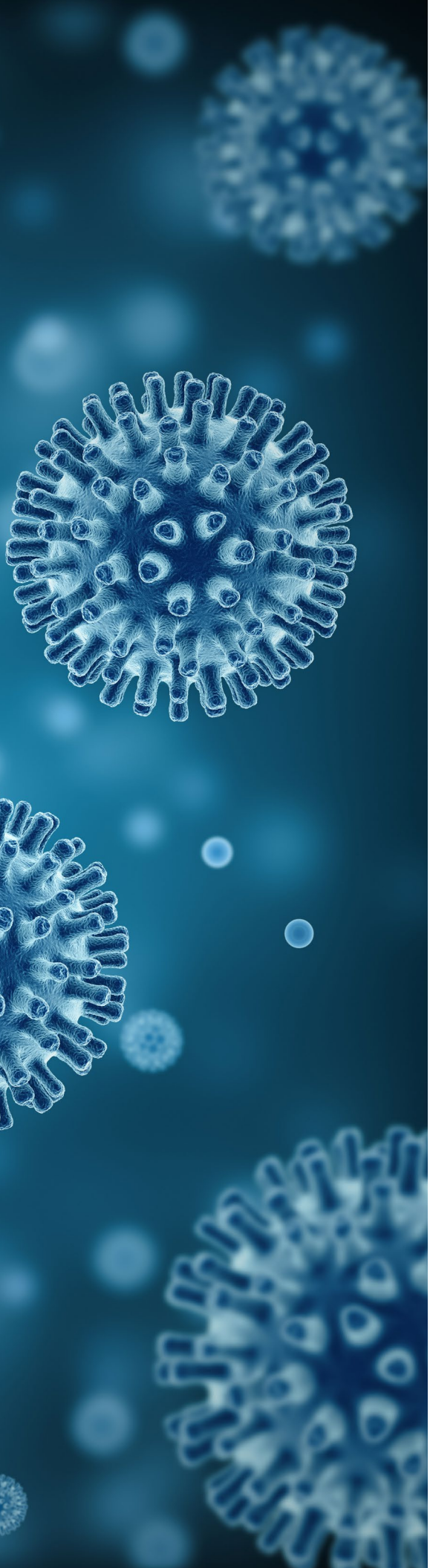
Different strategies are being explored, including chemical modification of the actual oligonucleotide, implementation of lipid or polymeric nanocarriers and linking oligonucleotides to receptor-targeting agents such as carbohydrates, peptides or aptamers. Off-target impacts have also been a historical and ongoing concern, but much progress has and is continuing to be made.



Regulatory Complexity

The typical factors for development of oligonucleotide regulatory guidance are obvious: significant potency/efficacy, stability in vivo, favorable pharmacokinetics (PK), favorable pharmacodynamics (PD), minimization of off-target effects and safety. However, oligonucleotide drugs fall somewhere between small molecules and large-molecule biologics, creating a new set of unique regulatory challenges.

Oligonucleotides are chemically synthesized, and despite the diversity within this class of drugs, there are similarities in approaches for synthesis. However, there is tremendous range in the mechanics of action of these drugs at the cellular level. At the core of the debate is the reality that oligonucleotides are manufactured in ways similar to other small-molecule drugs, but interact in vivo in a manner more typical of biologic therapies. From an efficacy standpoint, recognition that the class of oligonucleotide therapeutics is quite unique has contributed to significant advances in the field at a therapeutic/clinical level. Applying tailored solutions based on the characteristics of the molecules rather than attempting to find a likely nonexistent universal solution for targeting and cell uptake is the required path. While this approach has helped a great deal to advance oligonucleotide therapeutic technologies, progress has been slow in figuring out how to apply this to regulatory constructs and creation.

Despite the challenges in creating regulations for oligonucleotide therapeutics, the FDA has released recommendations for approaching synthetic oligonucleotide drug substance and drug product approval—"Points To Consider For The Submission of Chemistry, Manufacturing, and Controls (CMC) Information in Oligonucleotide-Based Therapeutic Drug Applications."

In addition to the lack of firm regulations, there is disagreement among the FDA and the European Medicines Agency (EMA), the world's leading drug regulatory bodies, as to how oligonucleotides should be approached for regulatory purposes. After some debate, the FDA decided to classify these drugs as small-molecule drugs and they fall under the FDA's Center for Drug Evaluation and Research (CDER) jurisdiction.

However, in the EMA's view, there is a preference for the use of "centralized procedure" for oligonucleotide therapeutics rather than the "mutual recognition" procedure. The centralized procedure allows for marketing authorization throughout the European Union. The centralized procedure is required for drug products manufactured using biotechnological processes, orphan drug products and for drug products containing a new active substance which was not authorized in the community before May 20, 2004 (date of entry into force of Regulation (EC) No 726/2004) and which are intended for the treatment of AIDS, cancer, neurodegenerative disorder or diabetes.

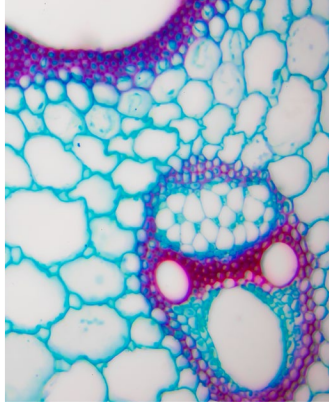
In contrast, any national marketing authorization granted by an EU member state's national authority can be used to support an application for its mutual recognition by other member states.

While disagreement on a core issue of this nature is far from ideal, given the promise these therapies represent for patient populations, there are reasons to be optimistic that this issue will find a resolution in time.

Q&A

with Tracy TreDenick

BioTechLogic Perspectives on Oligonucleotide Therapies



Q: Briefly describe the types of work you have done within the oligonucleotide space?

A: BioTechLogic has done a great deal of working with oligonucleotide products in recent years, including process validation work for drug substance, drug product and an oligo adjuvant.

Just some of BioTechLogic's oligonucleotide work has included:

- CMO on-site support
- Equipment qualification protocols
- Commercial-ready batch records
- Support validation protocols and studies
- Process validation
- Manufacturing support
- Technical support
- Facility validation reports
- Microbial monitoring strategies
- Commercialization plans
- Formulation development reports
- Process control strategies
- Chromatography column troubleshooting
- Multiproduct facility CV site policies and strategies

Q: What are the most common challenges you have confronted while working on oligonucleotide products, and how has BioTechLogic addressed these challenges?

A: One of the most common challenges is the environmental classifications for manufacturing this kind of product because in many situations, the product is not a finished product or an API, but an adjuvant. There are guidelines for drug products, and ICH Q7 for APIs, but not specific guidelines for adjuvants. BioTechLogic has had to evaluate the environmental requirements based on the needs of the product.

Another challenge is balancing the U.S. FDA filing requirements (macro-molecule) to the EU's "centralized procedure" which is used for biologics. For the most part, this challenge has been addressed by applying the most stringent of the two requirements, allowing the given product to be filed both in the United States and in the European Union (EU).

Q: Share your views on the oligonucleotide product regulatory debate, including the likely issues that will surface on the regulatory landscape as these products mature.

A: The U.S. technical/regulatory experts for oligonucleotides say these are just macro-molecules, a type of large "small molecule," as opposed to a biologic. A biologic is typically difficult to characterize using analytical procedures, while small molecules are far easier to characterize. There is some debate about impurities and quality assurance when manufacturing oligonucleotide products; however, via improved analytical instrumental technologies and new approaches, the industry has made a lot of ground here. But typically, the difference in regulatory environment amounts to what type of manufacturing support validation that you have to do for a biologic as opposed to a small molecule, and there is generally more complex work for a biologic.

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