In recent years, the peptide drug discovery field has shown a high level of dynamism, with hundreds of academic groups working on this topic, the creation of new peptide-focused companies, and the consolidation of peptide business by so-called big pharma [1–4].

In the last five years (2015–2019), the U.S. Food Drug Administration (FDA) have authorized a total of 208 new drugs (150 new chemical entities and 58 biologics) [5,6], 15 of which were peptides or peptide-containing molecules (Table 1), which account for 7% of the total number of drugs [4,7]. This is a rather impressive number, if we consider the efforts of the pharmaceutical industry in peptides in comparison to small molecules (in the context of this work, a peptide is defined as a compound that contains two or more amino acids linked by an amide (peptide) bond and that can be synthesized chemically).

The chemical structure and medical indication of the active principle ingredient of these drugs show an excellent representation of the diversity of the peptide world.

From a chemical structure perspective, it is possible to find small peptides (Ninlar®, Macrilen®); medium-sized peptides (Giapreza®, Scenesse®); homodetic (through amide bonds) cyclic peptides (Vyleesi®); intra- and intermolecular disulfide-containing peptides (Parsabiv®, containing almost exclusively D-amino acids; Trulance®); large peptides (Tymlos®, Lixisenatide®), which in some cases are branched (Ozempic®, Tresiba®); and peptides containing radionuclides [Lutathera®, 68Ga DOTA-TOC (68Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid-D-Phe1-Tyr3-octreotide)]. In the case of the two antibody drug conjugates (ADC) PADCEV® and Polivy®, the payload is the peptide monomethyl auristatin E (MMAE), a synthetic analog of the marine natural peptide dolastatin 10. MMAE is also the drug contained in Adcetris®, which was approved by the FDA in 2011. Of the seven FDA-approved ADCs to date, three contain a peptide. Moreover, PADCEV® and Polivy® contain the dipeptide Val-Cit as a linker. Another peptide-based linker, Gly-Gly-Phe-Gly, is present in the ADC Enhertu®, which was authorized by the FDA in 2019.

Oncology, with five drugs (two radio peptides and two ADCs), metabolism (three), and endocrinology (two) are the most frequent medical indications for peptides. However, cardiovascular conditions, gastroenterology, bone diseases, dermatology, and sexual dysfunction are also targeted by peptides.

Of note, between 2015 and 2019, several of the new peptide-based drugs accepted by the FDA came about from the efforts of academic groups. This highlights the importance of fostering solid and efficient cooperation channels between academia and industry with the aim to maintain and improve the well-being of society.
In addition to the use of peptides as drugs or in diagnostics, these molecules are playing an increasingly important role as drug delivery systems and as the base for new biomaterials with broad potential applications in medicine.

Table 1. Peptide-based drugs approved by the Food Drug Administration (FDA) (2015–2019) [3–6].

| Year | Active Ingredient | Trade Name | Indication | Features |
|------|-------------------|------------|------------|----------|
| 2015 | Insulin degludec  | Tresiba®   | Diabetes   | Modified insulin with an aa deletion and a hexadecanedioic acid via γ-Glu at the Lys (B29) |
| 2015 | Ixazomib         | Ninlar®    | Multiple myeloma | N-Acylated, C-boronic acid dipeptide |
| 2016 | Adlyxin Lixisenatide® | Lixisenatide® | Diabetes | 44 aa GLP-1 peptide with (Lys)₆ at the C-terminal |
| 2017 | Abaloparatide    | Tymlos®   | Osteoporosis | 34 aa analog of parathyroid hormone-related protein |
| 2017 | Angiotensin II  | Giapreza® | Hypotension | Natural octapeptide |
| 2017 | Etekcalotide    | Parsabiv® | Hyperparathyroidism | Ac-DCys-DAla-(DArg)₃-DAla-DArg-NH₂ linked to L-Cys through a disulfide bridge |
| 2017 | Macimorelin     | Macrilen® | Growth hormone deficiency | Pseudotripeptide N-formylated |
| 2017 | Plecanatide     | Trulance® | Chronic idiopathic constipation | 16 aa with two disulfides |
| 2018 | Semaaglutide    | Ozempic®  | Diabetes | GLP-1 peptide (31 aa in the chain) with hexadecanedioic acid via γ-Glu and mini PEG at Lys |
| 2018 | 177Lu DOTA-TATE | Lutathera® | Neuroendocrine tumors, theranostic | 177Lu chelated by DOTA bound to Tyr3-octreotate |
| 2019 | 68Ga DOTA-TOC   | Neuroendocrine tumors, diagnostic | 68Ga chelated by DOTA bound to Tyr3-octreotide |
| 2019 | Afamelanotide  | Scensese® | Skin damage and pain | 13 aa lineal peptide analog of α-MSH |
| 2019 | Bremelanotide  | Vyleesi®  | Women hypoactive sexual desire | 7 aa cyclic peptide analog of α-MSH |
| 2019 | Enfortumab Vedotin-Ejfv | PADCEV® | Cancers expressing Nectin-4 | ADC with a synthetic analog of the marine natural peptide dolastatin 10 |
| 2019 | Polatuzumab Vedotin-Piiq | Polivy® | Diffuse large B-cell lymphoma | ADC with a synthetic analog of dolastatin 10 (5-residue peptide alcohol) |

This analysis supports the strength of peptides in the medicinal field. In this context, we have decided to publish a Special Issue in Molecules, termed “Peptide Therapeutics 2.0”, which contains excellent quality research articles and comprehensive reviews on peptides. It is hoped that some of the peptides introduced herein will reach the market in the coming years.

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