Peptide Drugs of the Decade

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INTRODUCTION

"Peptide Highlights" is replete with interesting examples of natural and synthetically produced peptides which give promising results in early *in vitro* or pre-clinical animal studies and appear destined to be marketed as medicinal substances. The impression is of a bewildering array of peptide molecules available to treat disease.

The process of drug development from laboratory to patient however, is a challenging obstacle course for a potential therapeutic peptide, which like any other drug, has to be proven both safe and effective in clinical trials before obtaining marketing authorisation.

As the approaching end of a decade prompts us to look back and review trends, it is interesting to view peptide development from the regulatory angle and find answers to questions such as "How many peptide therapeutics received marketing authorisation over the last ten years?", "How does this number compare with the previous decade?" and "Can we detect any trends in therapeutic peptide development?" This article will attempt to shed a little light on these questions. Exclusion/inclusion criteria for the purposes of the data collection are those adopted by Lau & Dunn (2018), except that peptides derived from non-recombinant bacterial fermentation are included (e.g. daptomycin is included).

PEPTIDE DRUGS ON THE MARKET

There are currently some 60-70 approved peptide drugs in the US, Europe and Japan, over 150 in active clinical development and 260 having been tested in clinical trials (Lau & Dunn, 2018). Specifically, over the last decade, 2010 to 2019 (last update 12-12-2019), the US Food and Drug Administration (FDA) granted marketing authorisation to a total of 18 peptide drugs; this was out of a total of 372 new molecular entity (NME) authorisations over the same period (Figure 1, Table 1). This compares with 18 peptide drug out of a total of 235 NME authorisations over the previous decade 2000-2009.

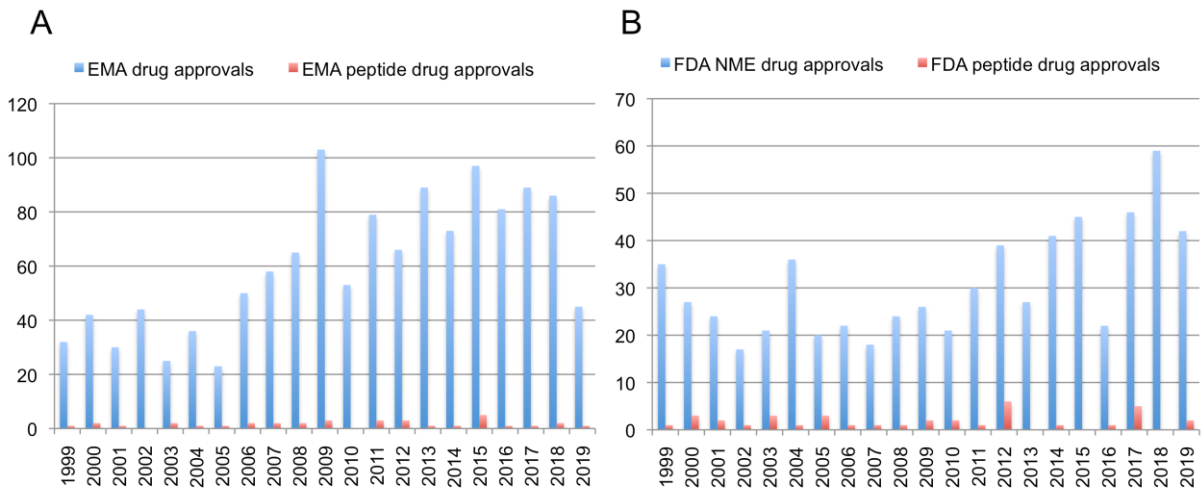


Figure 1. A. EMA peptide vs. total number of marketing authorisations for medicinal products for human use 1999-2019. (Taken from the Union Register of medicinal products for human use [last update 12-12-2019]: https://ec.europa.eu/health/documents/community-register/html/index_en.htm). B. FDA peptide drug vs NME authorisations 1999-2019. (Taken from CDER calendar year approval lists: https://www.fda.gov/drugs/nda-and-bla-approvals/nda-and-bla-calendar-year-approvals. Data for 2019 [last update 12-12-2019]: https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019).

When we look at the EU, the number of peptide drugs receiving marketing authorisation is similar to the US, and there is overlap, albeit incomplete, of approved peptide drugs in the US and Europe. The European Medicines Agency (EMA) granted centralised marketing authorisation to 18 peptide drugs over the decade 2010-2019 (to 12-12-2019) (Table 2). Of these 18, two have since been withdrawn, leaving 16 active peptide drugs approved by EMA over the recent decade. This compares with 16 peptide drugs which obtained EMA centralised market authorisation over the

previous decade, 2000-2009. From the European Register of Medicinal Products for human use, the total number of central authorisations for medicinal products for human use for the period 2010-2019 stands at 758 and for the previous decade 2000-2009, at 476. The difference between the number of FDA and EMA approvals is explained by the fact that the FDA publishes lists for novel drugs exclusively (NMEs), whereas the EMA approval lists include generics. (This is one example of the differences between the US and EU concerning drug approval, which complicates direct comparisons between the two markets, as has been remarked upon elsewhere [BioEurope Spring, 2019]).

The main conclusion from these data is that, against a background of increasing numbers of total drug approvals in Europe and the US, the number of peptide drug approvals has remained virtually steady from the previous decade 2000-2009 to the current one, 2010-2019 (Table 1).

Table 1. Peptide drug approvals in Europe and the United States over the last two decades.

Decade	Peptide drug approvals		All drug approvals	
	US	EU	US (NMEs)	EU
2010-2019	18	18	372	758
2000-2009	18	16	235	476

EVOLUTION OF PEPTIDE DRUG DEVELOPMENT

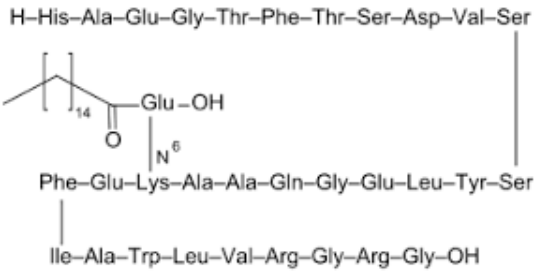
Six of the peptide drugs granted marketing authorisation by EMA over the decade 2010-2019 also have orphan drug status, giving them an added 10 year market exclusivity compared to other drugs (Table 2). This compares to only one orphan drug approval in the previous decade (ziconotide [INN], Prialt, authorised February, 2005). The dramatic increase in orphan drug approvals reflects the incentives offered to companies developing drugs for orphan conditions, and has the positive outcome of therapies becoming available for patients suffering from rare diseases.

Concerning indications for which peptide drugs are developed, a wide range is observed, but type 2 diabetes mellitus is the most frequent, reflecting the growing problem of obesity in modern society (Ricci, 2018). Three of the 18 peptide drugs approved during the decade 2010-2019 are therapies for diabetes. This compares with two peptide drugs approved for treatment of diabetes in the previous decade 2000-2009 (exenatide [INN], tradename Byetta, approved November 2006 and liraglutide [INN], tradename Victoza, approved July 2009).

The development of peptide drugs to treat diabetes illustrates how these drugs continue to increase in complexity with time (Fosgerau & Hoffmann, 2015; Al Musaimi, 2018). Liraglutide, is a 31-amino acid peptide analogue of the human glucagon-like peptide-1 (GLP-1) and acts as a GLP-1 receptor agonist, differing from the human glucagon-like peptide by the addition of a palmitoyl chain attached to Lys26 (of the wild-type GLP-1) through a Glu side chain linker:

Human glucagon-like peptide 1, 92-128:
>sp|P01275|92-128
HDEFERHAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG

>Liraglutide Sequence
HAEGTFTSDVSSYLEGQAAKEEFIAWLVRGRG



The presence of the 17-carboxyheptadecanoyl fatty acid moiety results in its binding to human albumin, which is responsible for the longer-acting activity of liraglutide in comparison with other members of the GLP-1 receptor agonist family (Al Musaimi, 2018). Liraglutide is currently produced by recombinant DNA expression of its peptide precursor in yeast. Peptides of the length of liraglutide represent the upper limit in size for the stepwise solid phase peptide synthesis (SPPS) strategy first developed by Merrifield in the early 1960s (Merrifield, 1963). Modifications of SPPS employing novel resins show promise for commercial synthesis of longer peptides such as liraglutide (Carbajo, 2019) in the future.

Table 2. Novel peptide drugs which received centralised marketing authorisation from the EMA during the period 2010-2019 (15-11-2019 update)(Diagnostics excluded; "w", withdrawn; "o", orphan drug status). Data from the European Commisssion Community Register of medicinal products: https://ec.europa.eu/health/documents/community-register/html/index_en.htm

Active substance INN	Product Tradename (EU)	Indication	Date of EU centralised marketing authorisation	Marketing Authorisation Holder
Afamelanotide	Scennesse	Prevention of phototoxicity in adults with erythropoietic protoporphyria	29-12-2014 (o)	Clinuvel Europe Ireland
Angiotensin II acetate	Giapreza	Refractory hypertension	27-8-2019	La Jolla Pharmaceutical The Netherlands
Boceprevir	Victrelis	Chronic hepatitis C	19-7-2011 (w)	Merck, Sharp & Dohme UK
Carfilzomib	Kyprolis	Multiple myeloma in adults	23-11-2015 (o)	Amgen Europe The Netherlands
Ciclosporin	Ikervis	Severe keratitis in adult patients with dry eye disease	23-3-2015	Santen Oy Finland
Ciclosporin	Verkazia	Severe vernal keratoconjunctivitis in children over 4 years and adolescents	10-7-2018 (o)	Santen Oy Finland
Dalbavancin	Xydalba	Acute bacterial skin and skin structure infections in adults	23-2-2015	Allergan Pharmaceuticals International Ireland
Etelcalcetide	Parsabiv	Secondary hyperparathyroidism in adult patients with chronic kidney disease	15-11-2016	Amgen Europe The Netherlands
Exenatide	Bydureon	Type 2 diabetes mellitus	23-6-2011	Astra Zeneca AB Sweden
Linaclotide	Constella	Moderate to severe irritable bowel syndrome	28-11-2012	Allergan Pharmaceuticals International
Lixisenatide	Lyxumia	Type 2 diabetes mellitus	5-2-2013	Sanofi-Aventis France
Lutetium (^{177}Lu) oxodotreotide	Lutathera	Somatostatin receptor positive, gastroenteropancreatic neuroendocrine tumours	28-9-2017 (o)	Advanced Accelerator Applications France
Ombitasvir (paritaprevir and ritonavir)	Viekirax	Chronic hepatitis C	19-1-2015	AbbVie Germany
Oritavancin	Orbactiv	Acute bacterial skin and skin infections in adults	23-3-2015	Menarini International Operations Luxembourg
Pasireotide	Signifor	Acromegaly Cushing"s disease	27-4-2012 (o)	Novartis Europharm Ireland
Semaglutide	Ozempic	Type 2 diabetes mellitus	12-2-2018	Novo Nordisk Denmark
Teduglutide	Revestive	Short bowel syndrome in patients older than one year	4-9-2012 (o)	Shire Pharmaceuticals Ireland
Televancin	Vibativ	Nosocomial pneumonia associated with MRSA	6-9-2011 (w)	Theravance Biopharma Ireland

Semaglutide (INN), tradename Ozempic, approved February 2018, was developed by Novo Nordisk as an improvement of liraglutide. Compared to liraglutide, semaglutide has a longer (C-18) fatty acid moiety attached to Lys26, which increases drug-binding to albumin; Ala8 (of the wild-type GLP-1) is replaced with 2-aminoisobutyric acid which renders the peptide refractive to peptidase attack; Lys34 is replaced with arginine as in liraglutide. These modifications of semaglutide give it a much longer plasma half-life compared to liraglutide, allowing administration frequency to be reduced to once weekly subcutaneous injection (Figure 2; Table 2). Novo Nordisk received FDA approval for an oral formulation of semaglutide, tradename Rybelsus, in September 2019.

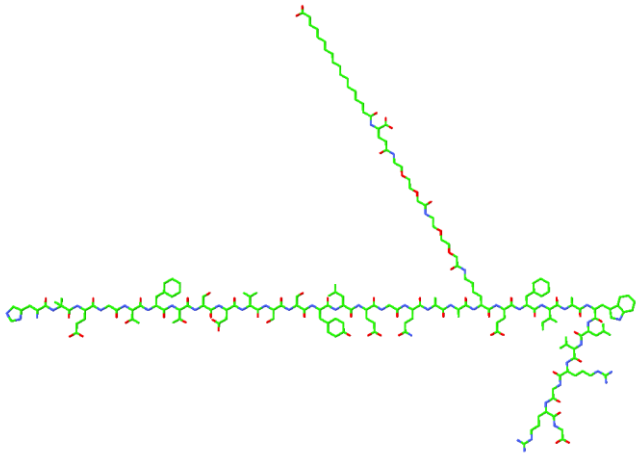


Figure 2. Structure of the peptide drug semaglutide, tradename Ozempic, approved by EMA on 12-2-2018 for treatment of type 2 diabetes mellitus. (Source: DrugBank: www.drugbank.ca; Wishart, 2018).

Lixisenatide (INN), tradename Lyxumia, another GLP-1 receptor agonist developed by Sanofi-Aventis, was approved by EMA in February 2013 for treatment of diabetes mellitus (Table 2) and was subsequently incorporated into a formulation in combination with insulin glargine (INN), approved by EMA in January 2017, tradename Suliqua, for the same indication.

Cyclosporin (INN), first discovered by Sandoz in 1970 is a lipophilic polypeptide of 11 amino acids presenting powerful immunosuppressive and immunomodulatory properties (Lallemand, 2017). Cyclosporin, isolated from the fungus *Beauveria nivea,* was first formulated as an injectable solution in 1980. Surprisingly, we see cyclosporin cropping up again in two authorisations of the recent decade (Table 2). The Finnish company Santen Oy was granted marketing authorisation for Ikervis in February 2013 for treatment of severe keratitis and for Verkazia in July 2018 for the orphan condition severe vernal keratoconjunctivitis in children older than 4 years and adolescents. This is a good example of how an already known, yet extremely effective drug can be re-marketed with a new niche indication.

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