Challenges for Therapeutic Peptides Part 1: On the Inside, Looking Out

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In the first of a two-part article, the challenges faced by the peptide manufacturing industry are reviewed from an insider's standpoint.

Therapeutic peptides have taken a long time to come of age. Many of the early peptide-based therapeutics were obtained from animal tissue. The first chemical synthesis of a therapeutic peptide was that of oxytocin in 1953. Recombinant synthesis of proteins was introduced in 1974, and recombinant human insulin, the first approved peptide therapeutic to be manufactured by recombinant fermentation, was introduced in 1982. All-in-all, about 65 peptide-based drug products have reached approval, with over 75 per cent of these coming in the last three decades.

The year 2012 will probably see another seven to eight new peptide drug products being approved, which is over twice the number approved in any previous year (see Table 1). The number of new peptide-based drug products achieving approval, and also the widening range of medical indications, underlines the increasing maturity of peptides as a class of pharmaceutical actives.

Keywords

Therapeutic peptides
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Formulation issues
Alternative delivery platforms
Manufacturing costs

Perceived Challenges

In spite of the increasing rate of approval, therapeutic peptides as a drug class still face significant challenges. They are generally perceived as being:

- Rapidly eliminated *in vivo*, unless chemical modifications are made (true)
- Expensive (debatable)
- Labile during storage at ambient temperatures (generally true)
- Not normally orally available, requiring injection by needle and being associated with self-administration compliance issues (true)

These challenges might read like a list of independent hurdles, but if a peptide-based drug is to be designed rationally to achieve success, all these challenges seem to us – *insiders looking out* – to be intimately inter-related and should be addressed together in a more holistic approach early in any drug candidate life cycle. Unfortunately, this is not normally the case. Most candidates take off as default 'injectables' and, having started down that path, reach later stage clinical development with a number of built-in formulation issues, which remain unresolved until post-approval modifications can be made. Changes in formulation or delivery modality in late clinical trials can put the approval process at risk, so many decisions that will profoundly affect the market success of the drug product need to made early in development.

The 'Most Desired' Peptide Product

So what does the 'most desired' peptide drug product look like? Although there are exceptions, such as human parathyroid hormone (hPTH), luteinizing hormone-releasing hormone (LHRH for fertility) and other peptides that have to be administered in a pulsatile manner to have efficacy, there is little doubt that the preferred therapeutic form would be a tablet or capsule containing a long-acting peptide drug that is stable at ambient temperatures and costs no more – or slightly more – than the injectable equivalent. Although an oral formulation may not always be possible, other non-parenteral or alternative delivery platforms may be more than adequate to achieve a suitable drug form, sufficient efficacy and satisfactory compliance. There is never going to be a single set of guidelines for reaching that goal, but a rational evaluation of the intended drug and its eventual market at the start of the development campaign can help achieve this.

Table 1: Approved peptide drugs products since 2000

Second approvals of drug substances (for example Exenatide as Byetta in Europe in 2011) are not included

Approval year	Location	Generic name	Brand name	Company	Indication	Route	Dose*
2000	EU	Atosiban	Tractocile	Ferring	Premature labour	IV	< 330mg
	US	Bivalirudin	Angiomax	Medicines Company	Unstable angina	IV	250mg
	NZ	VIP	Aviptadil	Senatek	Erectile dysfuncyion	AI**	25µg
2001	US	Nesiritide	Natrecor	Scios	Congestive heart failure	IV	1.5mg
	US	Triptorelin	Trelstar	Debiopharm	Hormone-responsive cancer	IM	3.75mg
2002	US	Teriparatide	Forteo	Lilly	Osteoprosis	SC	20µg
2003	US	Abarelix	Plenaxis	Praecis	Prostate cancer	IM	113mg
	US	Enfuvirtide	Fuzeon	Roche	HIV-1	SC	90mg
2004	US	Zicontide	Prialt	Elan	Severe and chronic pain	IT	100µg
2005	US	Exenatide	Byetta	Amylin	Diabetes, Type 2	SC	10µg
	US	Pramlintide	Symlin	Amylin	Diabetes, Type 1 and Type 2	SC	15µg
2007	US	Lanreotide	Somatuline LA	Ipsen	Agromegaly	IM	30mg
2008	US	Degarelix	Firmagon	Ferring	Prostate cancer	SC	120mg
	EU	Icatibant	Firazyr	Jerini	Hereditary angioedema	SC	30mg
2009	EU	Liraglutide	Victoza	Novo Nordisk	Diabetes, Type 2	SC	1.2mg
2010	US	Tesamorelin	Egrifta	Theratechnologies	Lipodystrophy in HIV	SC	2mg
2012	US	Sinapultide	Lucinacant	Discovery	RDS in premature infants	ITD	> 1mg
	EU	Pasireotide	Signifor	Novartis	Cushing's disease	SC	600µg
	US	Peginesatide	Omontys	Affymax	Anaemia in CKD with dialysis	SC	~20mg
	US	Carfilzomib	Kyprolis	Onyx	Refractory multiple myeloma	IV	60mg
2012 (pending at	EU	Afamelanotide***	Scenesse	Clinuvel	Erythropoietic protoporphyria	SC	16mg
time of press)	US	Linaclotide	Linzess	Ironwood	Constipation in IBS	PO	266µg
	EU	Lixisenatide	Lyxumia	Sanofi-aventis	Diabetes, Type 2	SC	10µg
	US	Teduglutide	Gattex	NPS	Adult short bowel syndrome	SC	~5mg

* Where possible minimum single dose (not necessarily daily dose) is listed – some doses are weight-dependent

** Autoinjector

*** Pre-approved in Italy in 2010

The Right Peptide Form

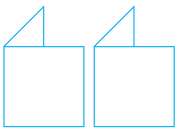
The first question has to be whether the chosen peptide in its present form is a suitable candidate for treating its intended indication. If the peptide is eliminated rapidly *in vivo,* as most native sequences are, chemical modifications to the peptide, either within the sequence or by conjugation to a polymer or a lipid, need to be considered to obtain a therapeutic candidate that is less easily degraded or less amenable to renal clearance. There is now a wide range of natural and synthetic polymeric conjugates available, including: polyethylene glycol (PEG), hydroxyethyl starch (HES), human serum albumin (HSA), XTEN (a recombinant polypeptide), PAS (a recombinant polypeptide containing only proline, serine and alanine), polyglutamic acid and monoclonal antibodies.

By making a covalent modification, a new chemical entity (NCE) is created that may have markedly different pharmacokinetic (PK), pharmacodynamic (PD) and immunogenic characteristics. If the conjugation is reversible, the active pharmaceutical ingredient (API) will have the nature of a pro-drug, which does not need to interact directly with the drug target; if it is non-reversible, then interaction with the target is mandatory. Covalent conjugation typically reduces potency, but this should be more than compensated for by the extended half-life.

An alternative approach is to incorporate the peptide into a biodegradable long-acting release (LAR) matrix, such as a poly D, L-lactide-co-glycolide (PLGA) polymer, or a hydrogel. Because the release profile of an LAR matrix can be designed, it is possible to programme biphasic or multi-phasic release; this is useful, for example, for administering a vaccine and its booster in a single dose. Modifications will also usually add to the cost of the final drug product and the cost-benefit advantages need to be assessed carefully.

Market Assessment

When the drug candidate has been selected, it is important to assess the estimated final dosage and size



Peptides are relatively expensive drug substances, especially if quantities are low. However, there are very significant economies of scale as batch size is increased and the commercial costs should be carefully evaluated before making decisions based on development-scale lots.

of the initial commercial market as this will influence the choice of manufacturing technology, and contract manufacturing organisation (CMO) or internal resources, with the appropriate capacity, capability and regulatory experience to support the campaign requirements. Because the drug loads of the various alternative delivery devices available differ significantly, an approximate knowledge of the intended dose range enables decisions to be made on the use of a particular delivery platform – if any. If an alternative delivery platform is being considered, it should be remembered that most systems that use trans-mucosal delivery usually show significantly lower bioavailability (when compared with subcutaneous injection) and will require larger dosages. Bioavailability normally decreases with increasing chain length. Knowledge of the commercial market will enable the sponsor to calculate the cost per dose and allow assessment of the market viability of the drug product.

Cost Considerations

Peptides are relatively expensive drug substances, especially if quantities are low. However, there are very significant economies of scale as batch size is increased and the commercial costs should be carefully evaluated before making decisions based on development-scale lots. While precise calculation of very large scale (multi-10 or multi-100kg) manufacture is not possible during the development stage, most competent GMP vendors will be able to provide realistic estimates on pricing from grams to multi-10 kg quantities or more.

The concept that peptide-based drugs are expensive in relation to other drug classes is often more perceived than real, although it can certainly be true for 'high dose, long sequence' scenarios. Ultimately, it is the cost per dose that counts. There is no reason why a short sequence peptide should be more expensive than a small molecule with the same number of synthetic steps when manufactured at the same scale. Many longer peptides have a complexity similar to biologics that command significantly higher unit costs. Indeed, up to about 50 amino acids (even at the multi-10kg scale), synthetic chemistry is usually significantly more cost-effective than recombinant technologies for GMP manufacture. Moreover, many long peptide drug candidates have exceptionally high potency which translates into a low dose cost even when the gram unit cost is high. The emergence of cost-effective scalable technologies for peptide production, combined with highly efficacious peptides, will play a significant role in the development of oral and other alternative delivery technologies once believed to be the sole domain of small molecules.

In Part 2 of this article, which will be published in the next edition of *IPT*, we address alternative delivery platforms for administering peptides – including the 'Holy Grail' of oral administration – and look at whether the use of novel delivery systems can be justified in terms of their 'added value'.

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