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Review

Peptides as Drugs: Is There a Market?

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INTRODUCTION

The first synthetic peptide was prepared by Emil Fischer a century ago, but the medicinal use of synthetic peptides started after the Second World War, and only when peptides could be prepared pure by du Vigneaud's group in the USA, and by the Swiss industrial groups of Robert Schwyzer (Ciba) and Huguenin (Sandoz). This was the time of oxytocin and vasopressin, cyclic nonapeptides with one disulphide bridge, and of the angiotensins. The synthesis of peptides was a long and difficult task, a single peptide taking 1–2 years to produce by conventional methods. It was the genius of Bruce Merrifield, in 1963, who hastened and automated this long process using the method he named Solid Phase Peptide Synthesis (SPPS). The acceptance of the method was rather fast, helped by the development of new purification methods (HPLC) which allowed purification of some incredible mixtures.

From the 1960s to the end of the Millennium, peptides were often considered as the drugs of the future. Their main drawback was their low bioavailability. Further, some major pharmaceutical companies, which had invested heavily in peptide projects, had to drop some of these in the late clinical phase. This led them to develop the concept of peptidomimetics with working principles such as 'no secondary amide group' or 'no molecular weight over 600', which almost killed the field. But many Biotech companies discovered new peptides with interesting pharmacological properties, and SPPS was optimized, allowing the routine synthesis of large polypeptides or small proteins from 30–100 amino acid residues: peptides were saved. But are they really the hoped-for miracle, and what is their meaning in today's drug market?

This review will not be fully objective, because it is written by a peptide chemist who has devoted all his professional life to the field, and who hopes that it will awake some future careers.

ETHICAL PHARMACEUTICAL MARKET

In 2000, the total ethical pharmaceutical market was worth about USD 265 billion with a yearly growth of 11%, meaning that in 2001 the market must be close to USD 290 billion. Within that market, the peptides and proteins, excluding vaccines, reached USD 28 billion in 2000 and will surely be very close to USD 31 billion in 2001. The number of new chemical entities (NCE) has been almost stable for about 10 years with around 35–40 each year, but the number of peptide and protein NCEs has been increasing during recent years.

It is important to note that the figures given here are for sales to the end patients in the final dosage forms of the drugs, and not the cost of the chemicals.

PEPTIDES AND PROTEINS

In the global class of peptides and proteins as defined above, the recombinant proteins have a

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Editorial note: The author made a contribution on this theme to the 17th American Peptide Symposium in San Diego, June 2001. One of our Editorial Advisers was so impressed that he suggested that it should be developed into a review for our Journal. The author himself was diffident and modest, thinking that what he had gleaned from his sources and presented in San Diego was likely to be out of date by the time it appeared in print. He yielded to persuasion, however, for which we are grateful — the sort of background information he presents is very difficult to find in the formal scientific literature.

BIOGRAPHY

Albert Loffet The author graduated in 1965 from the University of Liège in Belgium. He then joined UCB R&D in Brussels, where he created the peptide group. From 1977 to 1984 he was the manager of UCB-Bioproducts, then moved to France where he started Propeptide in 1985. When this subsidiary of SNPE was integrated into Isochem in 1996, he joined Senn Chemicals, where he is presently Director of Marketing and Sales. He organized the 14th European Peptide Symposium in 1976 and was Secretary of the EPS from 1988 to 1994.

share of about 50%, USD 14 billion. The monoclonal antibodies segment of the market is probably the fastest growing reaching USD 4 billion in 2000 and will most probably already have reached USD 5 billion in 2001. However, it took over 20 years from the concept to its first really important therapeutic application, despite its use as a diagnostic reagent which had been developed many years before (1978).

The chemically synthesized products account for about USD 10 billion together with ACE inhibitors and the first generation of HIV protease inhibitors. The category of 'classical' peptides has reached USD 4 billion. The market for the APIs (active pharmaceutical ingredient) plus the products that are in development account for roughly USD 400–450 million. This figure is expected to double in the next five years.

THERAPEUTIC CLASSES

Peptides and proteins are used in many indications and can be used in various therapeutic classes. The following is a list of therapeutic classes where at least one product was in phase I; this does not concern products considered to be in R&D or pre-clinical phases.

Allergy and asthma	Analgesia
Antivirals	Arthritis

Baldness	Calcium metabolism
Cancer	Cardiovascular
CNS	Diabetes
Epilepsy	Gastrointestinal
Growth	Gynaecology
Haemostasis	Immunity
Impotence	Incontinence
Inflammation	Obesity
Ophthalmology	Pain
Tumour imaging	Vaccines

DIAGNOSTIC

Peptides have been used as diagnostics for a long time, but this market has always been considered as marginal because of the small volumes of product involved. Hormonal diagnostics are now widely used for all the releasing hormones: TRH, LH-RH, Somatostatin, GH-RH. These peptides have to be injected and are thus treated almost as classical drugs. Viral diagnostics also use some peptide antibodies and the corresponding antigens, but this is an *in vitro* use as a peptide substrate, used for instance to check the proteins involved in the coagulation cascade. Tumour imaging is a diagnostic tool, but can also lead to therapeutic applications. It could reverse the current opinion about peptides as diagnostics, as the number of cancers which are diagnosed each year is important. This market could be even larger if, for instance, systematic screening for breast cancer and prostate cancer were to be introduced.

RECOMBINANT PROTEINS

Over 50 recombinant proteins are already on the market, and some of the products will soon lose their patent protection and become generics.

By 50 products, I mean 50 different chemical compounds and not different formulations of the same compound.

The main proteins on the market are:

Erythropoietin	Interferons α and β
Insulin	Interleukins
Growth hormone	Gonadotropins
Hirudin	Coagulation factors
Growth factors	Enzymes

In pre-registration and phase III there are more than 40 products, which is a significant pipe-line, as are the 60 products that are now in phase II. The number of other proteins at a very early stage of development is even higher. Many companies are investing heavily, as they believe that there will be a shortage of production capacity. A very interesting point is that some illnesses which are considered as 'orphan', such as Gaucher's or Fabry's disease, are nevertheless economically attractive, and give rise to huge competition between Biotech companies.

MONOCLONAL ANTIBODIES

Marketed: >20 products
Pre-registration and phase III: >20 products
Phase II: >45 products

This is the fastest growing segment of the peptide and protein market, as new humanized monoclonal antibodies are being tested in almost every possible therapeutic application. The first potential 'blockbuster' in this category is the GpIIb/IIIa inhibitor Reopro (Eli Lilly). Even though the number of marketed products appears to be rather small, the pipe-line is really impressive, especially at the early stages of development, as there are over 100 products on which clinical testing has started.

SYNTHETIC PEPTIDES

Marketed: >40 products
Pre-registration and phase III: >20 products
Phase II: >60 products

This class of products, which embraces all peptides and peptidomimetics made by chemical synthesis, will now be discussed in more detail.

Gonadorelin Super-agonists

These peptides are used in endocrine cancers, especially in prostate and breast cancers. The main products are listed below:

Leuprolide	Abbott TAP
Buserelin	Aventis
Zoladex	AstraZeneca
Triptorelin	Ipsen Beaufour
Nafarelin	Roche

The total class accounts for over USD 2 billion and involves about 150–200 kg of active substances.

Most of these compounds are now generics, but have not yet been replaced, for instance by gonadorelin antagonists. This market will obviously increase in the next few years with the development of new slow-release formulations, such as the titanium implant recently introduced by Alza which offers a single 1 year treatment.

Somatostatin Analogues

The sales of products in this class were over USD 900 million with quantities smaller than 100 kg. The therapeutic indication is also cancer, but is linked to the anti-growth effect of these somatostatin agonists. Two main products are on the market:

Octreotide	Novartis
Somatuline	Ipsen

Both of them have recently been launched in the USA with a long-lasting formulation.

These products will soon become generics, but the new formulations recently registered will give them several years of life without any problem.

ACE Inhibitors

Most of the time the angiotensin converting enzyme inhibitors have not been considered as peptides, even by peptide chemists, as they are mainly substituted dipeptides which have been produced in very large volumes by conventional organic synthesis. But is peptide synthesis not a specialized branch of organic chemistry?

The best known members of this family are Enalapril and Lysinopril, both from Merck and both blockbusters. Even if their glory is now fading with the introduction of the new non-peptide angiotensin II receptor antagonists, they are still widely used products. Other well-known products in the class are Ramipril, Trandolapril and Perindopril. The total class of ACE inhibitors has about 15 launched products with sales of over USD 4 billion, with quantities over 100 tons, in huge contrast of scale to the gonadorelin super-agonists.

HIV Protease Inhibitors

The sequence of the HIV protease was, of course, deduced from cDNA sequences but it was the synthesis by Steve Kent and Dan Veber which allowed the precise determination of its enzymatic activity and the design of synthetic substrates for testing. The crystal structure was also established from synthetic material, and this allowed, firstly, the design of peptide inhibitors, and then of modified peptides, which could in a sense be considered as peptidomimetics even if they still incorporated peptide motifs. The first HIV protease inhibitor to reach the market was Roche's Saquinavir, shortly followed by Merck's Indinavir and Abbott's Ritonavir. This first generation was followed by a second which had somewhat less peptidic character, as for example Agouron's (now Pfizer) Nelfinavir. The sales of this class of product is over USD 1.5 billion with quantities over 200 tons. The third generation now under study is really non-peptidic, but has yet to be launched, and will arrive on the market more than six years after the 'peptidic' products, when many people are already suffering resistance to this kind of therapy. Is this really a bonus?

Vasopressin Analogues

Vasopressin is an old product which was first synthesized at the end of the 1950s. Use of the natural product has been very low in contrast to that of some of the analogues, mainly discovered by the Prague school of Josef Rudinger and developed as drugs by Ferring. The best known agent of this family is Desmopressin, (des-amino-D-Arg^8-vasopressin). Its main use is now for enuresis. Other members of the family are Terlipressin (triglycylvasopressin), Lyspressin and Felypressin. Altogether the sales are over USD 300 million for quantities not much over 50 kg.

Calcitonins

Osteoporosis-treating drugs are now very important in our Western ageing world, but even if new products have been launched recently, calcitonins are still available and used. The three main products are salmon, human and eel calcitonin. It had been reported that human calcitonin was 10 times less active than salmon calcitonin but this happened to be an experimental error as both products are equipotent. There was a belief that this rather large peptide (32 amino acids) would be produced by recombinant technology in place of synthetic chemical methods. However, even if the methods were described there was no complete development, and no recombinant calcitonin was launched, contrary to another well-known target of the Ciba peptide group, human insulin. The total sales of the class nevertheless is worth about USD 500–600 million with pure APIs being at a level of a maximum of 50 kg.

Immunostimulating Peptides

During the mid 1980s the peptide that was produced in the largest quantity was thymopentin, a sequence of one of the immunostimulating thymic hormones that was produced in quantities of up to 400 kg. However, the drastic changes in reimbursement policies of most countries in which it was registered led to its withdrawal. Another thymic hormone, thymosin α-1, is, however, still used in Southern Asia, Middle East and South America. Another immunostimulating glycopeptide has been marketed in Russia: Glucosaminylmuramyl dipeptide, (GMDP), but the quantities produced are still relatively small — only a few kg yearly.

Other Peptides

Older peptides such as the natural human angiotensins and oxytocins, as well as ACTH-(1-24), are still produced and marketed. The total sales are only about USD 200 million, with quantities probably much lower than 100 kg.

Gonadorelin Antagonists

The 'super-agonists' family of LH-RH agonists has been successfully used for over 20 years in prostate cancer and for other endocrine tumours. Their main disadvantage is a surge of LH and FSH after administration, obviously followed by a surge in testosterone or oestrogens for about 1 week, before the full depletion of the hormones which allows for control of the tumour growth. It was therefore believed that antagonists, which in animal models did not elicit this testosterone surge, would be obvious replacements for the agonist therapy.

However, to obtain a satisfactory inhibition of testosterone release the injected dosage was approximately five to ten times higher than that for the best agonists. This brought about problems in the design of slow release formulations, which need to be competitive, not only in terms of cost but also in sustained release for the available 3 and 6 months therapies. With most of the clinical studies in cancer treatment having failed, only two antagonists up to now have been launched for different indications: Cetrorelix and Ganirelix are both used for the treatment of gynaecological disorders and in *in vitro* fertilization, which is a much smaller market than the hormone dependent cancers.

NEWLY LAUNCHED PRODUCTS

Several peptidic NCEs have been launched in recent years:

Integrilin is a cyclic heptapeptide developed by Cor Pharmaceuticals and marketed by Schering-Plough, which is the first GpIIb/IIIa inhibitor of its class. It competes directly with Lilly's Reopro humanized monoclonal antibody which has the advantage of being launched a few years before Integrilin, but is much more expensive. The number of indications in which Integrilin has been approved is increasing, and even if it is not a 'blockbuster', its sales, which are expected to reach USD 250 million in 2001, are significant.

Atosiban is an oxytocin antagonist launched by Ferring on the European market after it had failed FDA approval following clinical trials led by Johnson and Johnson. It is used to suppress premature contractions in pregnancy. The availability of other cheap therapies do not allow Atosiban to take a significant part of the market.

Bivalirudin is the hirudin analogue first developed in the early 1990s by Biogen, but was stopped for economic reasons, the activity of the product having never been in doubt. It was taken over a few years ago by The Medicine Company, who have succeeded in registering the product in New Zealand. Bivalirudin was approved last year by the FDA and launched in the USA; its approval in Europe is pending. Its blood clot dissolving activity is of great importance when emergency treatment has to be given.

VIP has also been approved for the treatment of erectile dysfunction but it is hard to believe that it could become a competitor to Pfizer's Viagra.

Techtide P829 and Groliberin (GH-RH) have been registered as diagnostic agents.

Taltirelin is a TRH analogue devoid of endocrine activity but active on the CNS; it was recently launched by Tanabe in Japan.

Also awaiting registration are: Montirelin, another TRH analogue from Gruenenthal used in the CNS; Ziconotide, a conotoxin peptide used in analgesia for which a long-lasting formulation, is developed by Elan.

PRODUCTS IN PHASE III

Qualification of a product in phase II or III is not always apparent. In fact some products are in phase

III in a few countries, while the bulk of the phase II trials are still in progress.

At the time of writing the following products were still in phase III, at least in some countries:

Pramlintide, for treatment of diabetes: an FDA final decision is expected by December 2001 but the non-approval recommendation issued by the FDA expert committee is a severe drawback for Amylin.
Protegrin, an antibacterial, was put on hold due to a non-approval letter from the FDA, but recent discussions seem to be more positive.
Abarelix is the first LH-RH antagonist to have been filed with the FDA as a cancer therapy; the non approval letter issued by the FDA has been a threat to the entire peptide community. Discussions with the FDA will continue, but the recent decision of Amgen to cancel its agreement with Praecis does not allow much optimism.
SPC3, which is a MAP (Multiple Antigen Peptide), is in phase III for HIV treatment but it does not seem to awake a lot of interest in the major companies involved in the marketing of AIDS drugs.
Ambamustin for treatment of cancer is also in phase III.
SF-250 which is an anti-infectious agent has fast track review process and is now in phase II for acne treatment.
Pentafuside is the first product of a new class of HIV cell entrance inhibitor. Discovered by Trimeris (T-20) and licensed for co-development to Roche, it is the first peptide to be produced on an industrial scale by solid phase using a very interesting strategy using Fmoc synthesis of three fragments which are then assembled in solution to make the final 36-mer peptide. The forecasts of production if the product is launched range from 1 to 5 tons of peptide. The quantities of Fmoc amino acids, coupling agents and 2-chlorotrityl chloride resin required have already revolutionized the field in giving it a more mature industrial structure.
Posatirelin is a TRH analogue from Dainippon, designed for CNS action.
Sinapultide is a surfactant developed by Discovery Laboratories for respiratory distress syndrome.

Other products are Valpreotide, a somatostatin analogue; Fibrimage, a contrasting agent, IM-862 (H-Glu-Trp-OH), an angiogenesis inhibitor under investigation by Cytran; and Gastrimmune, a vaccine based on Gastrin-(1-17).

Betabloc, the Alzheimer potential therapy in development by Elan, is in phase II but is expected to move to phase III soon.

ADVANTAGES AND DRAWBACKS OF PEPTIDES

The advantages of peptides as drugs are as well known as their disadvantages. Let us summarize them:

- High activity, which usually means that small doses of peptide have to be administered, and also the total amount to be produced is relatively small.
- Peptides are usually highly specific and have therefore relatively low systemic toxicity. They do not accumulate in the body as they have relatively short half-lives.
- Their low bioavailability has the consequence that they have to be injected or special formulations have to be designed to accommodate them.
- The cost of their synthesis has also been considered disadvantageous. This could change with larger scale availability of all the products needed, (protected amino aids, coupling reagents, resins) and also of the equipment and products used in the purification.

NEW FORMULATIONS

Solving the problem of injection of peptides, and proteins, has been the theme of much research and development for many years.

New formulations can be of various kinds:

- Biodegradable polymers
- Non-degradable implants
- Liposomes
- Transdermal injection
- Inhalation
- Polymer coated pellets for oral administration

There are over 50 companies specializing in formulation, but not all of them are interested in peptides or proteins. However, the following companies are developing technologies which can be used for such compounds and generally have one or more products in the clinical phase:

Alkermes	Altea
Alza	Aronex
Aradigm	Atrix
Debio	Dura
Elan	Emispheres
Inhale	Nobex
Powderject	Skye Pharma

CONCLUSIONS

The market for peptides and proteins is a healthy one. The triggering of specific receptors, or modulation of enzymatic activity, can be done in a potent and specific way using these refined tools. However, synthetic peptides still suffer from a deficit in image 'because they have to be injected'.

As if erythropoietin or insulin had to be taken orally to be a blockbuster!

Times will probably change because solid phase synthesis will be used more and more, allowing easier production of relatively long peptides or short proteins.

In the case of emergency treatments the speed of action and the low side-effects of a peptide injection is unbeatable.

Surely chronic treatment with new formulations will also give a new impetus to the field.

It is my strong belief that deciphering the way in which proteins act (proteomics is now the fashionable word instead of genomics) will give rise to more and more opportunities to finding new active peptides which will become new drugs. And finally, I would like to give this advice to newcomers to the field: think big, and do not stick to the dogma of small molecules: insulin has yet to be replaced on the market, even if has to be injected more than once a day!

SOURCES

Most of the information given in this review was compiled from publications such as Scrip, Chemical Engineering News, Chemical Market Reporter, Bioengineering News etc and also from databases such as Pioneer, Drugs of the Future, or Pharmaprojects. All the information needs cross-checking and while every care has been taken no responsability is accepted for any unaccuracies.