400
300
200
100

Therapeutic Peptides under the Spotlight

Catherine Pichereau and Claude Allary at Bionest explore the challenges, trends and opportunities within a sector receiving increasing attention

Catherine Pichereau is a Finance Practice Leader for Bionest Partners, an independent boutique offering consulting and advisory services for health care companies. Since joining Bionest Partners in January 2004, Catherine has been committed to the development of the financial advisory franchise. Catherine began her career in the corporate finance teams of Robertson Stephens (London, UK) and Bank of America Securities (London, UK), entirely dedicated to health care. She worked on M&A and private placement transactions for European companies, including biotechs, specialty pharma and medtechs. Catherine graduated from HEC business school (Paris, France) with additional qualifications from the Stockholm School of Economics (Stockholm, Sweden) and the Vienna University of Economics and Business Administration (Vienna, Austria).

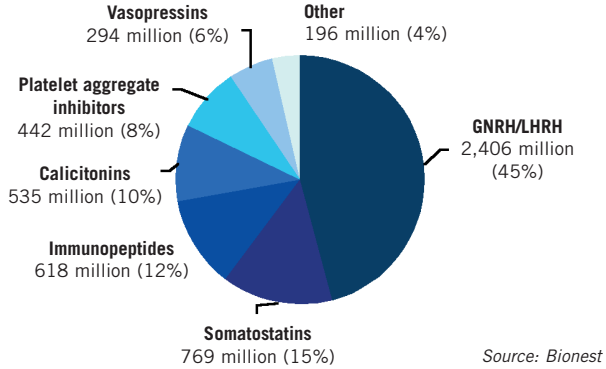
Claude Allary is a founding Managing Partner of Bionest Partners. After 17 years spent in the international pharmaceutical industry with Rhône-Poulenc, Parke-Davis and Glaxo plc London, where his last position was Director, International CNS Product Development, he moved into management consulting in 1991. He spent eight years with Arthur D Little in London, Brussels and Paris, followed by four years with ISO Health Care Group (part of the Monitor Group of companies) before founding Bionest Partners in 2002. Claude has been involved in over 130 consulting projects spanning R&D, strategy and organisation in pharmaceuticals, biopharmaceuticals, medical devices and diagnostics. He is a frequent contributor to professional journals and congresses.

Peptides are an interesting bet for R&D companies. Their role as mediators of key biological functions and their unique intrinsic properties make them particularly attractive therapeutic agents: peptides show high biological activity associated with low toxicity and high specificity. The benefits conferred by these characteristics include little unspecific binding to molecular structures other than the desired target, minimisation of drug-drug interactions and less accumulation in tissues reducing risks of complications due to intermediate metabolites. Additionally, compared to small molecules, peptides offer valuable chemical and biological diversity on which intellectual property is still widely available. As a result, even the big pharmaceutical companies, traditionally focused on small molecules, are increasingly considering peptides in their pipelines (for example Pfizer, GSK and Lilly have recently acquired peptide-based products).

AN EMERGING MARKET

The therapeutic peptides market emerged in the 1970s, when Novartis launched Lypressin, a vasopressin analogue. Since then, approximately 30 peptides have reached the market, representing a €5.3 billion opportunity in 2003 (over 1.5 per cent of the €325 billion global pharmaceutical market). Among the different classes of peptides, GNRH/LHRH agonists (leuprorelin, goserelin) account for almost 50 per cent of the market. Other key commercialised peptides include sandostatin (somatostatin analogue, Novartis), glatiramer (immunomodulator peptide, Teva), salmon calcitonin (Miacalcin, Novartis) and desmopressin (DDAVP, Ferring) (see Figure 1).

Figure 1: Key Classes of Therapeutic Peptides (2003)



Source: Bionest

Figure 2: Therapeutic Peptide Pipeline (January 2004)

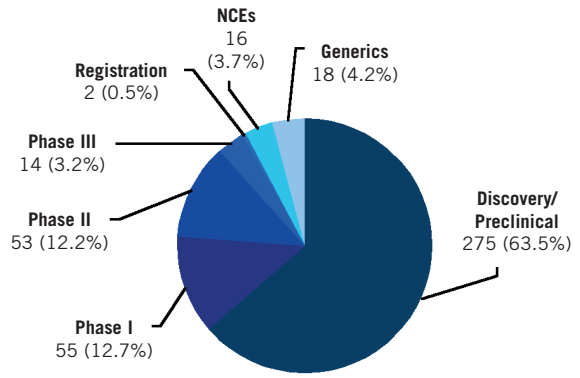


Table 1: New Peptide Developments

Peptide Enhancing Technologies

- Glycosylation
  - Addition of carbohydrate chain, gels, polymeric implants
- AA Sequence Modification
  - Addition of non-natural amino acids
- Pegylation
  - Addition of polyethylene glycol (PEG) molecules
- Cyclisation
  - Disulphide bond between two cysteine residues, or by head-to-tail or side-chain cyclisation, forming an amide bond

Peptide Delivery Technologies

- Parenteral Route
  - Controlled release subcutaneous, intramuscular or intravenous (emulsions, microspheres/microparticles, nanospheres/nanoparticles/nanocapsules)
- Mucosal Route
  - Nasal spray
  - Pulmonary delivery (active or passive inhalers, micronised by powders)
  - Oral delivery (sub-lingual caplets)
- Oral Route
  - Penetration enhancers (fatty acids, surfactants)
  - Protease inhibitors
  - Carriers: nanoparticles, microspheres, liposomes
- Transdermal Route
  - Patches
  - New delivery devices (phonophoresis, iontophoresis and so on)

Source: Bionest

The majority of peptides currently on the market are generics with relatively low growth potential. In fact, few truly innovative peptides have reached the market over recent years due to several inherent limitations including: peptides generally suffer from low stability (quick degradation and clearance from the body); low oral bioavailability (injection required); difficult delivery (cross-membrane transportation); risk of immunogenic effects; as well as challenging and costly synthesis (solubility issues) and so on. Hence, recent R&D efforts have been focused on improving the pharmacological activities and bioavailability of peptides (see Table 1). Several peptide modifications have been shown to improve peptides' *in vivo* half-lives significantly: the addition of carbohydrate chains, non-natural amino acids, polyethylene glycol molecules as well as the addition of a disulphide bond between two cysteine residues. Sustained release delivery systems have also been developed. Finally, new drug delivery technologies have emerged, including oral, nasal and pulmonary.

MEDIUM TERM GROWTH POTENTIAL

Today, it seems that years of fundamental research are finally about to bear fruit. Renewed interest in peptides has led to a soaring number of projects in development. Within just a few years, the pipeline of therapeutic peptides has grown significantly. In January 2004, there were 400 peptides in development globally; almost three times as many as in September 2001 (see Figure 2). And while the current pipeline is still primarily driven by early-stage projects (discovery/preclinical stages), an increasing number of peptides are maturing into later stage trials and reaching the market. Several key therapeutic peptides were recently launched on the market, including: platelet aggregation inhibitors bivalirudin (Angiomax, The Medicines Company) and eptifibatide (Integrilin, Millennium); HIV cell entry inhibitor enfuvirtide (Fuzeon, Roche); and GNRH antagonist abarelix (Plenaxis, Praecis). Moreover, projects in Phase II/III have grown from 24 in September 2001 to 67 in January 2004.

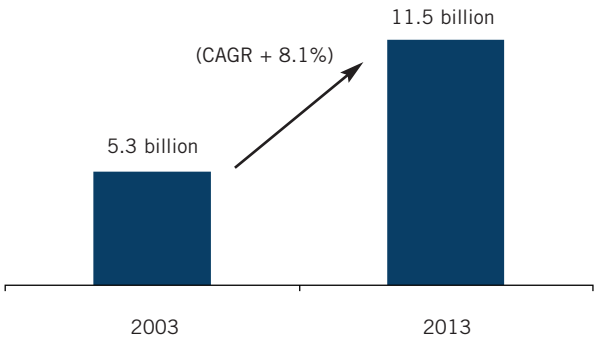
Thus, peptides are expected to enjoy fairly attractive growth rates in the short- and medium-term. Analysts estimate an eight per cent compound annual growth rate over the next decade (see Figure 3, page 90). In particular, four projects have been identified as significant short-term growth drivers (see Table 2). Currently in the Phase II/III

Table 2: Near-Term Peptide Market Growth Drivers

Generic Name	Trade Name	Company	Current Status	Estimated Launch Date	Peak Sales
AC-2993	Exenatide	Amylin/Eli Lilly	Approved	2005	>€600m
Thymosin	Zadaxin	Sciclone	Phase II/III	2007	€500m
Degarelix	n/a	Ferring	Phase II/III	2008	€400m
AC-2993 LAR	Exenatide LAR	Amylin/Eli Lilly	Phase II	2009	>€1,200m

Source: Bionest

Figure 3: Therapeutic Peptide Market Growth (03-13)



Source: Bionest

stage, they could reach cumulated peak sales of over €2 billion, which would represent almost 50 per cent of the current market size.

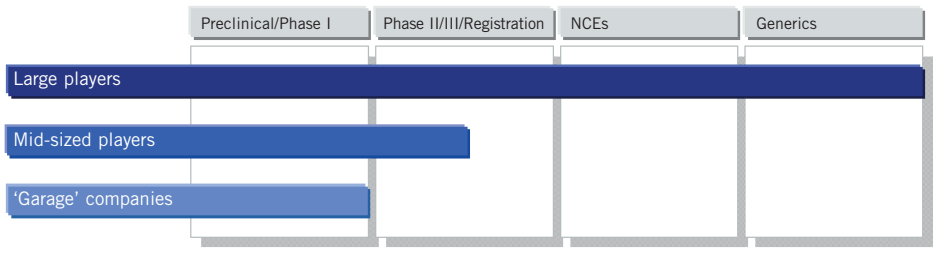
THE NEED FOR PEPTIDE API CONTRACT MANUFACTURERS TO CONSOLIDATE

Mostly due to significant capital expenditure requirements, R&D companies increasingly outsource the production of their peptides to contract manufacturers, thereby contributing to the development of a specialised peptide CMO market. Today, the peptide API contract manufacturing market is fairly fragmented. Three main categories of peptide CMOs can be distinguished based on production capacity (see Figure 4). Seven large CMOs capture most of the market as only they can supply the high revenue-generating Phase III and commercial peptide API quantities required by R&D companies (up to several hundreds of kilograms). Based on several analyst estimates, Bachem, a Swiss public company entirely dedicated to peptide contract manufacturing activities, is the current market leader with approximately €100 million in sales. UCB Bioproducts, a division of Belgium-based UCB Group, is the likely runner-up, increasingly challenging Bachem. The company boasts a quickly growing franchise of commercial products, with several key clients including The Medicines Company (MDCO, Nasdaq), Praecis Pharmaceuticals (PRCS, Nasdaq) and Amylin Pharmaceuticals (AMLN, Nasdaq), and is thereby in a position to gradually impose its leadership. Polypeptide Laboratories, a Danish private company with a stronger focus on research ingredients and generics catalogues, is believed to rank third.

Four other CMOs are also competing in the large-scale production of peptides, namely Lonza, a Swiss public chemicals company, NeoMPS, a subsidiary of French-based chemicals and energetic materials company SNPE, Peptisyntha, a subsidiary of Belgium-based chemical and pharmaceutical group Solvay, and Diosynth, an Akzo Nobel business unit. Several so-called 'mid-sized' CMOs are also present on the market: they offer non-GMP as well as GMP production, however in fewer quantities than large CMOs (up to a few kilograms). They can typically produce peptide APIs throughout Phase IIa but are not usually able to support Phase III and commercial projects. Most are based in the US (American Peptide Company, AnaSpec, CS Bio, Phoenix Pharmaceuticals and so on). Last but not least, the market is also served by many small structures, usually referred to as 'garage companies', which solely address the small quantity early-stage peptide segment with non-GMP production services (milligrams to hundreds of grams). Over 100 have been identified to date, mainly located in the US and in Europe (a few are located in Asia).

As illustrated by NeoMPS, the product of the recent merger between Neosystem (France) and Multiple Peptide System (US), consolidation should also take place between large CMOs. As it happens, production capacity often remains a bottleneck for large CMOs, which can only handle a small number of commercial contracts simultaneously due to the large capacity utilisation they imply. As a result, a large part of their revenues is often heavily dependent on just a few contracts, which are also subject to high risk levels: R&D projects' attrition rates, demand volatility and so on. Hence, to reduce such exposure, large CMOs should look to diversify their customer base while increasing their production capacity. Consolidation can help to do just that.

Figure 4: Positioning of Peptide API Contract Manufacturers



Source: Bionest

INNOVATIONS TO COMBAT BOTTLENECKS

The battle to earn market share is fierce and likely to remain so. To survive and grow, CMOs have no choice but to dedicate resources to constantly innovate. First and foremost, efforts are being made to optimise current synthesis methods. For regular

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size peptides (50 residues), chemical synthesis remains the gold standard. Three main methods have been developed so far: the solid phase peptide synthesis (SPPS) or merrifield synthesis, the homogeneous phase peptide synthesis (HPPS) and the mixed phase synthesis (combination of solid and solution phase synthesis). However, several bottlenecks are hampering these processes. Let's for example consider the SPPS method: synthesis starts by attaching the first amino acid onto the resin, then additional amino acids are added one after another. This method thus involves a large series of deprotecting, linking, washing, re-deprotecting, relinking and rewashing steps, and requires regular monitoring. In addition, the high quantity of solvents, reagents, amino-acids and resins required generally drives CMO costs up. Efforts thus currently focus on improving productivity and costs.

Another synthesis bottleneck is often the lyophilisation step, which appears fairly time-consuming. Innovative technologies are being developed in this area. The production of longer peptides (100-150 residues) is also a challenge for CMOs. Mixed phase synthesis is currently preferred, but does not enable the efficient production of such peptides. Several CMOs are now developing new technologies to fill this gap: synthetic and recombinant (the latter being applicable to natural peptides only).

CMOs are also looking beyond synthetic technologies; Lonza was recently the first to apply recombinant technologies to peptide APIs. Catching other CMOs off guard, the manufacturer entered the peptide API contract manufacturing market as the only CMO offering recombinant technologies.

However, will Lonza convince late-stage and commercial R&D companies to switch to recombinant technologies? Despite significant potential in the synthesis of long peptide APIs (they best achieve folding, essential for a long peptide/protein to be biologically active) as well as the production of large quantities of peptide APIs (late-stage and commercial peptides), recombinant technologies are still in the making: besides non-negligible regulatory hurdles, production processes are deemed complex and product quality can sometimes be debated.

A NEW VALUE MODEL FOR CONTRACT MANUFACTURERS?

Could CMOs capture more value from peptides than they actually get from manufacturing services? This article outlines the potential of peptides in the pharmaceutical industry, but peptides also raise substantial interest in another health-related industry: the $3.5 billion anti-ageing cosmeceuticals industry. Dr Patricia Farris, a US dermatologist specialising in anti-ageing treatments, recently declared that peptides were "the new weapon against ageing and wrinkles". Indeed, cosmetic companies' ambition is to develop products with active ingredients that can rival the results of laser treatments or surgical facelifts. They are increasingly investigating peptides, which offer high potency at low dosages. Results came quickly: several peptides have now been launched on the market: Argireline (Lipotec), Matrixyl (Sederma) and Myoxinol (Cognis) – all Botox alternatives. Therapeutic Peptides, a private US company, is also developing two lines of peptides for use in skin creams and OTC anti-ageing products: Prolifersyn, a family of selected peptide fragments which stimulate collagen production, and Stimulysin, a family of small peptides that stimulate healing and destroy bacteria.

How could CMOs generate value from cosmetic peptides? As cosmetic companies buy peptides and use them at very low concentrations, pure cosmetic peptide CMO activities may not pay off. Still, specific synergies come to mind: CMOs benefit from privileged access to many peptides developed for therapeutic indications. Some may have strong potential as cosmetics. Would R&D companies want to retain absolutely all intellectual property rights on their prospective peptides knowing that they will focus solely on therapeutic indications? Or would they be willing to grant licenses covering cosmetic applications? An opportunity may very well lie here; CMOs could adopt a hybrid model combining a therapeutic peptide API contract services offering with the internal development of innovative cosmetics, thereby climbing up the value chain. In this respect, Spanish-based Lipotec may very well lead the way. ◆

The author can be contacted at catherine@bionest.com