A very bright future for cGMP-manufacturing of peptides

THOMAS VORHERR

Peptides have quite some history and as pointed out by Michael Chorev and Barry Morgan in the May issue this year *, the development of chemistry and analytical methods related to peptide synthesis has improved to an extraordinary level of expertise. This continuous methodological fine-tuning, supported by elaborated conditions for synthesis, by further development of chromatographic methods and advance in mass spectrometry technologies, enables professional peptide chemists to address the synthesis including the proof of homogeneity for even large peptides up to proteins.

DYNAMICS OF THE MARKET FOR RESEARCH-GRADE PEPTIDES

These achievements represent an excellent basis to efficiently provide high quality peptides and even small synthetic proteins, in particular for studies in the fields of genomics and proteomics. These approaches provide an enormous amount of data to rapidly expand our understanding regarding biochemical pathways and interfaces. Consequently, these activities will reveal a vast number of drug targets in the future. However, for target validation, the isolated compounds are needed to study in detail the specific task of proteins or protein families in the biochemical network. Therefore, synthetic peptides and small proteins, represent ideal tools to further investigate functional properties. In fact, a number of interesting molecules have already been identified and validated as drug targets. The synthetic availability of a bioactive peptide or a protein provides the basis for more detailed studies to understand in-depth how specific protein-protein interactions contribute to normal and pathological processing.
Furthermore, screening tools including library- and array-technologies have consolidated, and thus add standard repertoire for a fast lead finding process, the next step along the value chain in the drug discovery process.

Bachem Holding AG
Hauptstr. 144
CH-4416 Bubendorf, Switzerland

The majority of these recent technologies rely on the fast and efficient access to interesting peptide and protein sequences. According to this development, an increased request for research-based peptides is easily predictable. This view is supported by the fact that peptides and proteins accompany more closely than ever the lead finding process.
Nevertheless, there are other influential factors to be considered for predicting the future cGMP business involving manufacturing of peptides needed for clinical studies and a later commercialisation. Interestingly, the establishment of a large biotech scene and the progress in delivery technologies have led to a reassessment of peptides as drugs. Thus, a more positive view concerning historical critical factors has emerged recently, which should result in an enhanced interest to develop synthetic peptides and proteins as drugs. As a result, the need for cGMP manufactured peptides and proteins is likely to increase.

IMPLICATIONS FOR cGMP MANUFACTURING OF PEPTIDES

The value of peptides as drugs has been recognised for a long time and, clearly, part of their properties fit in the trend towards a highly potent and selective medication. For biopolymers like peptides, evolution has already realised highly specific and potent compounds. In this evolutionary process, side effects and toxicity have already been minimised and peptides have been adapted to fulfil a given task with utmost precision. This history and their importance for biological systems corroborate the potential of peptides and proteins as drugs. Although more than 30 peptides are on the market, basically two reasons have hampered a more widespread application.
In the past, larger pharmaceutical companies were not so much interested to address or to develop niche markets. According to the view of traditional medicinal chemistry, small molecular weight blockbusters had to represent the focus of big

* Peptide Forum - Mission and Objectives; chimica oggi - CHEMISTRY *TODAY* 21, 5, 6-7 (2003)

pharma's programs. However, the establishment of a large number of biotech companies and their recent success with respect to therapeutic antibodies and proteins has slowly changed this classical point of view.
A second drawback of peptides has been their low bioavailability and the need to use other but oral routes for administration. Over the last decade, more and more biotech enterprises have initiated lead finding and drug development projects. Most of them have concentrated on niche markets and due to their promising properties, peptides have become the centre of these companies' interests to target a specific indication either by a drug- or vaccine-approach. In the light of this focused interest, companies are even considering extra efforts to optimise bioavailability and, at the same time, they potentially strengthen patent protection of their products. Recent developments in the delivery of peptides and proteins, e.g. like a non-destructive particle-size reduction to enable bronchial passage, nasal applications, transdermal delivery or even oral administration by protecting the peptide from proteases encountered in the stomach, have led to considerable improvements with respect to stability and bioavailability.
In addition, the progress in synthesis has facilitated the incorporation of selective modifications into highly active peptides and proteins to increase their half–life. For example, a polyethyleneglycol (PEG) derivatisation slows down enzymatic degradation and makes the molecule to some extent resistant to renal clearance. Moreover, according to the FDA, PEG-derivatives are regarded as compounds safe for the use as a vehicle in foods, cosmetics and pharmaceuticals.
Although, most of these activities rather resided within the Biotech industries, Roche's recent deal with Gryphon Therapeutics to promote a synthetic protein, an erythropoietin analogue modified with PEG-chains, demonstrates the relevance of the latest improvements. In addition, another engagement with Trimeris regarding Fuzeon, a peptide developed as a drug to inhibit the first step of viral entry leading to HIV infection, the fusion of the membranes, indicates a paradigm shift with respect to the focus on small molecular weight drugs. The development of Fuzeon and the set-up of large-scale manufacturing capacity at Roche had tremendous effects on an entire industrial branch. In the course of this project, the global supply of amino acid derivatives and resins has undergone drastic changes and companies manufacturing starting materials are now ready to support any peptide synthesis project aiming at the ton scale. More generally speaking, a peptide-project for an important indication has paved the way for large-scale production of peptides since, in the first instance, capacity for manufacturing of starting materials has been built up.
Looking more closely at these events, it seems, pharmaceutical companies are systematically evaluating peptide/protein projects and even seriously consider a development of these biopolymers. The access to in-house or external proteomics facilities and the insights resulting from these investigations may contribute to this reawakened interest in peptides and proteins. Due to their availability early in the drug discovery process, peptides and/or proteins can also serve as a benchmark for potency and selectivity during the transformation into small molecules. As a matter of fact, peptides and proteins have already been recognised as potential drug candidates and in some cases, development has been carried out, especially for those projects in which the active principle could not be translated into a small molecular weight compound.
In the long run, the dynamic situation and enhanced interest of pharma companies in biomolecules, together with further improvements in the supply chain and delivery technologies, will clearly substantiate the demand for commercial cGMP manufacturing.
The increasing interest of the biotech environment and the growing number of important drug targets is already reflected in the number of clinical projects handled at Bachem. Bachem has secured >100 cGMP projects, more than ever in the history of the company, however, most of these projects are in early stage. Taking into account the limited number of peptide products so far launched in the market, the current overall-pipeline will lead to a substantial amount of commercial peptide products in the mid-term future. In general, these findings support the view of a revival of peptides and, in addition, confirm that the trend for outsourcing manufacturing to expert companies continues.
Clearly, cGMP manufacturers have to meet the following requirements: full compliance with current regulations combined with a rigorous quality control, e.g. to assure high purity, and flexibility, e.g. the ability to perform process development. Focusing on the flexibility issue and considering the current production process of Fuzeon, a successful manufacturer has to provide expertise in solution- and solid phase-methodology to be able to optimally adapt the process to the needs of the project. In more general terms this means, except the sole production, there are a couple of issues to be taken care of. Small companies concentrating on their core competencies would rather like to use resources in the most efficient way and prefer to include the professional management of problems related to manufacturing and registration in an entire production package. In this case, the customer enters in a more close relationship with a manufacturer and possibly benefits from a bundle of services designed to overcome the hurdles on the way through the clinical studies until approval. The ability to provide these additional services on the manufacturer side will be crucial to sustain business in the future. On the other hand, a manufacturer offering an integral service can significantly contribute to reduce time to market, a crucial issue for biotech- and pharma-companies. In addition to regulatory and other know-how, e.g. logistics, cGMP manufacturers have to provide sufficient capacity for synthesis and downstream processing to assure future production even after commercialisation of a peptide drug.
Regarding the increasing number of clinical peptide projects during the past years, as a logical next step, Bachem has already developed a plethora of the services needed to professionally accompany the production process and, due to the acquisition of Sochinaz SA in Switzerland, capacity for ton scale cGMP manufacturing has been made available.