



PEPCEUTICALS
Peptides | Antibodies | GMP Synthesis

Peptides | Antibodies | GMP Synthesis
PEPCEUTICALS



Certification No: PM560179

Pepceuticals Ltd
4 Feldspar Close
Warrens Park, Enderby
Leicestershire
LE19 4JS
UK

Tel: +44 (0)116 284 9301
Fax: +44 (0)116 286 2464

Website: www.pepceuticals.co.uk
Email: peptides@pepceuticals.co.uk





Pepceuticals, Experts in Peptide Synthesis

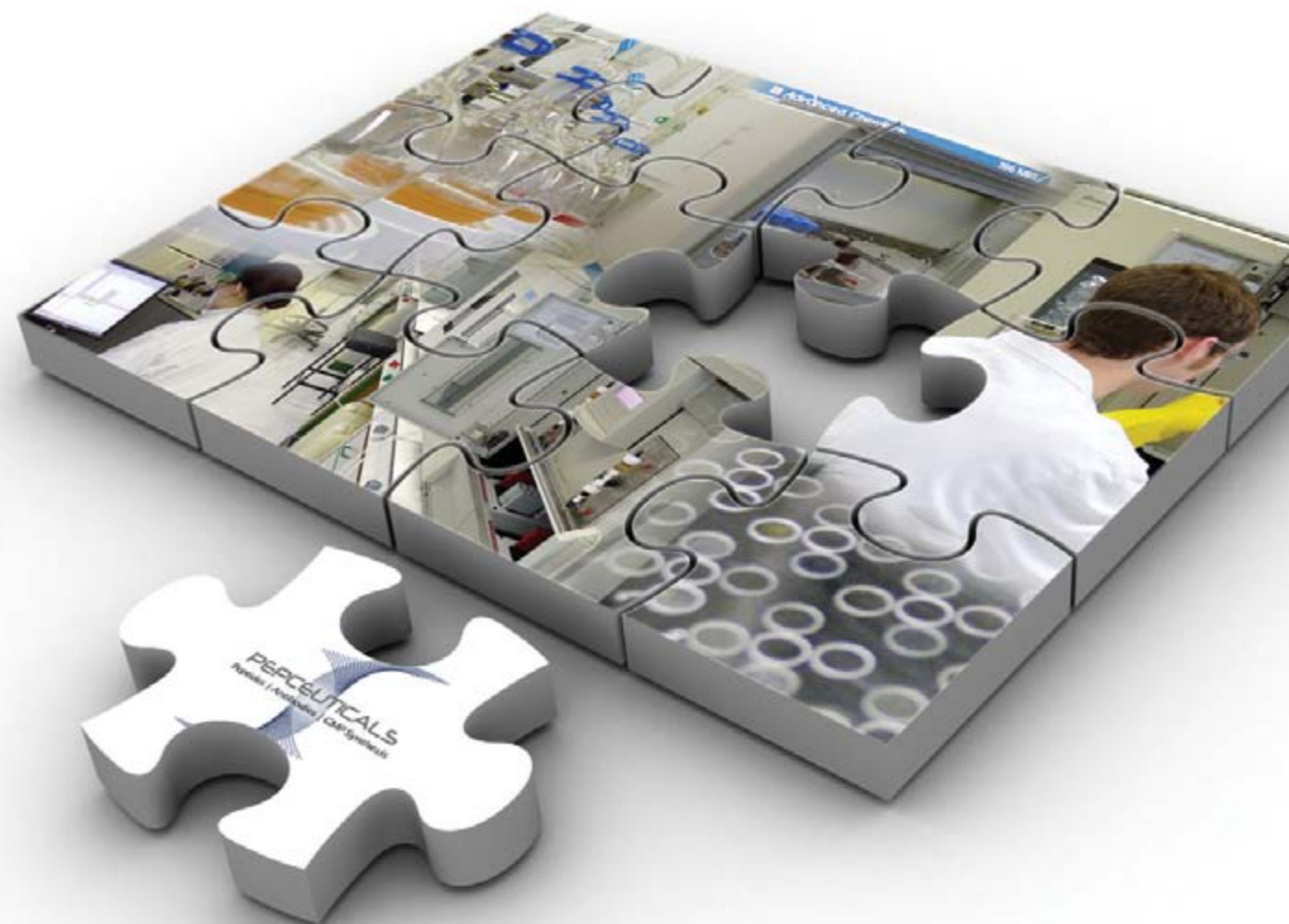
Pepceuticals Limited, established in 1998 as a manufacturer of synthetic peptides, is dedicated to supplying the Life Science industry with a high quality custom peptide and antibody service. In addition, we are also able to offer an extensive range of catalogue peptides and a wide range of reagents used for the synthesis of peptides.

Over the years Pepceuticals has established a reputation for excellence in the field of peptide synthesis, having developed novel technologies that allow us to prepare complex peptide molecules. Pepceuticals remains dedicated to providing a solution to the drug manufacturing industry, by continuing to increase its development program of large synthetic peptide libraries, enhancing the prospects of obtaining new drug candidates.

At Pepceuticals, we operate a stringent quality system which verifies that the products we supply meet or exceed industry standards. Our Quality Control (QC) team, ensure that our instrumentation, operating/ testing, and staff training are maintained and continually updated to achieve these high standards. Our aim is to deliver all our products in a reliable time frame with a full certificate of analysis and supporting data.

We believe that strong customer relations are the key to our success. Our team of highly qualified staff, are dedicated to providing an unrivalled customer service, ensuring effective project management and good communication with our clients, thus facilitating to promote and assist customer program planning.

From sales to product delivery we aspire to offer a complete solution. We trust that you will enjoy the benefits of working with Pepceuticals, as a reliable, flexible and innovative peptide manufacturer.



Pepceuticals: Your Perfect Fit

What we can offer

Pepceuticals provide custom synthesised peptides for the production of antibodies, labelled peptides for assay development and high throughput screening and cGMP peptides for use in clinical trial experiments.

Pepceuticals has the capacity and expertise to synthesise a large and diverse range of peptides whilst being dedicated to providing high quality products with fast turnaround times.

Capable of delivering research peptides on the milligram to kilogram scale, we use our own novel technologies to facilitate more efficient peptide synthesis, producing cleaner peptides. This allows us to confidently approach peptides up to 130 amino acids in length, and complete the projects in realistic timeframes.

Using our experience and industry-leading synthetic strategies, we prevail over difficult stretches in the peptide sequence, tackling synthesis problems before they occur.



A guide to peptide synthesis at Pepceuticals

Technical Design Analysis

At Pepceuticals we employ a range of methods to evaluate difficult peptides before synthesis. In doing so, we can successfully deliver peptide projects, faster.

Hydrophobicity plots - used to determine difficult stretches of amino acids in peptides.

Peptide Stability / Solubility - insolubility arises when the combined inter-/ intra-peptide ionic and hydrophobic interactions offset favourable peptide-solvent interactions.

Aggregation potential - a statistical analysis method which is used to determine which amino acid residues are likely to aggregate during peptide synthesis, leading to the formation of truncated peptide fragments.

Secondary structure formation - it is important to identify secondary structures formed during peptide synthesis. Using results of analysis we can employ synthetic protocols to disrupt their formation.

Molecular Modelling - a computation technique that allows us to look at the theoretical 3-dimensional structures of peptides. With this technique we can predict problematic amino acid stretches contained within peptides, thus allowing us to design the peptide strategy more effectively.

Our Peptide Capabilities

At Pepceuticals we employ a full range of continuous flow and batch synthesisers, as well as using manual and solution phase synthesis for the production of peptides. As part of our manufacturing capability we are continuously investing in the latest technology, so that we can cater for the increasing global demand for peptides.

Our automated synthesis equipment comprises:

- Continuous flow peptide systems
- Microwave peptide systems
- Multiple peptide synthesis systems

Peptide Length

We have developed novel peptide synthesis strategies that enable us to assemble long peptides. Our expertise in peptide synthesis allows us to offer peptides ranging up to 130 amino acids in length.

Quantity

Pepceuticals offers peptides to meet your various scale requirements, from milligrams to kilogram quantities.

Our Instrumentation Capabilities

Employing continuous flow and batch synthesisers, we are able to synthesise hundreds of peptides per week.

Continuous Flow synthesis

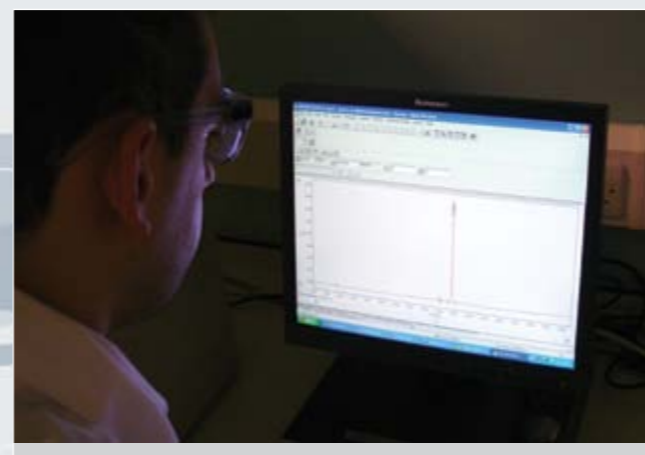
This method of peptide synthesis allows the peptide to assemble more efficiently and faster by removing excess reagents from the reaction chamber. This process is particularly suited to the synthesis of long and synthetically challenging peptides, as it allows good swelling properties of the peptide resin to be maintained during the synthesis process. As a result, peptide aggregation/ truncation is lowered, giving rise to higher purity peptides.

Batchwise synthesis

This method of peptide synthesis is compatible with Fmoc/ tBu and Boc/ Bzl methods, as well as a wide range of solid supports for peptide synthesis. This process is particularly suited to producing large peptide libraries in shortened turnaround times. Due to the processes involved in this type of synthesis, the resulting peptide quality is lower than that obtained from continuous flow synthesis.

Manual Synthesis

For complicated peptide sequences we can adopt a manual synthesis approach. We have successfully made glycopeptides, labelled peptides and branched peptides amongst others, using manual synthesis. Manual synthesis is more flexible than automated methods and usually results in a better crude peptide when compared to machine synthesis. At Pepceuticals we are able to utilise both methods and therefore are able to offer you advantages in automatic (cost and speed) and manual synthesis (complex peptides). We are also able to offer solution phase synthesis.

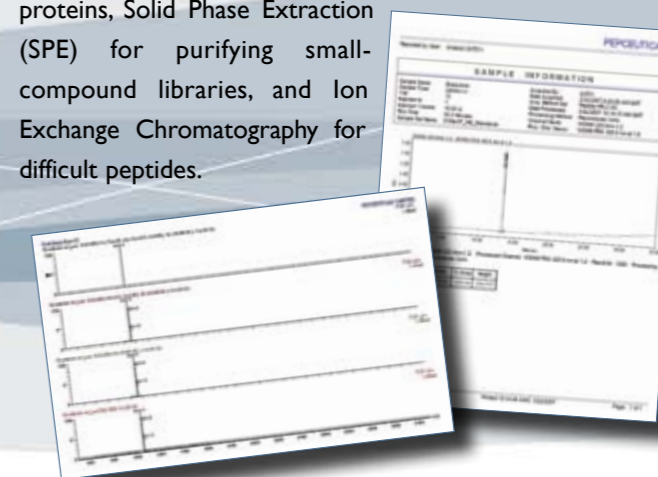


Peptide Purity

Purified grades

We are able to purify peptides to >99% as required by the customers specifications. The peptides are supplied with conforming documentation, such as an analytical HPLC chromatogram and mass spectrometry measurements.

Our purification suite is equipped with reverse phase HPLC equipment, both semi-preparative (milligram to gram quantities) and preparative (multi-gram to kilogram quantities). We are also able to adopt Fast Protein Liquid Chromatography (FPLC) for purifying large peptides and proteins, Solid Phase Extraction (SPE) for purifying small-compound libraries, and Ion Exchange Chromatography for difficult peptides.



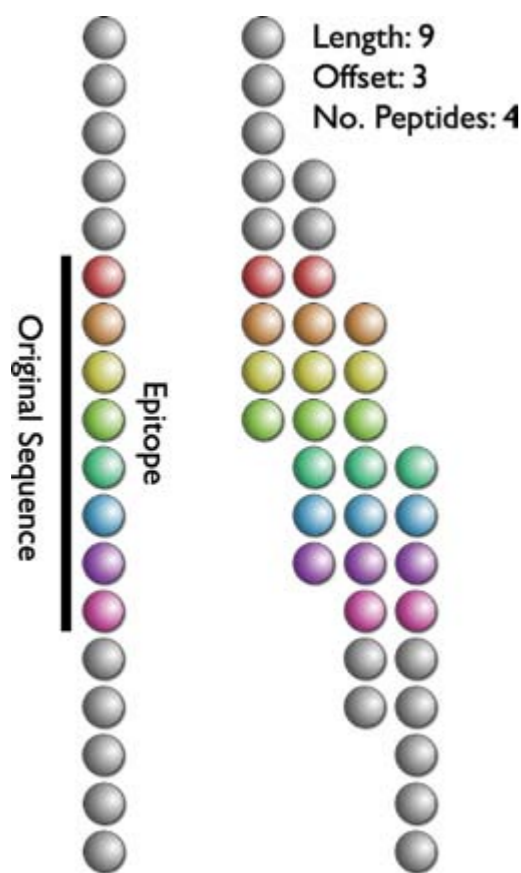


Peptide Libraries

For early stage drug development, and high throughput screening, we regularly prepare peptide libraries in different formats. We have developed synthesis technologies that allow us to prepare high quality peptides in low turnaround times, and at competitive prices.

Overlapping peptide libraries

Overlapping peptide libraries can be used for epitope mapping (linear and continuous), which can in turn be used to determine essential regions of a protein/ peptide contributing to the bioactivity. The library is designed based on two parameters: Peptide fragment length, and offset number. The peptide fragment length is the length of each peptide to be generated in the library, and is typically between 10 and 25 amino acids in length. The offset number is the degree of overlap with regard to the following peptide fragment.



Inert insertion scanning libraries (alanine, valine or leucine insertion)

Inert insertion scanning libraries, also known as alanine scanning libraries, are composed of a series of peptides in which one residue of the peptide backbone is systematically replaced with an alanine residue. The small methyl side chain of the alanine residue has relatively little biological activity and so a decrease in epitope activity is observed when an essential amino acid is replaced. In instances where size preservation is important, the amino acid may be replaced by a valine or leucine residue instead of an alanine residue.

Sequence scrambling libraries

Sequence scrambled libraries are composed of sequences containing (all) permutations of a given peptide sequence. This aids in peptide sequence optimization, and can be used to probe target molecules.

Positional importance scanning libraries

Positional importance scanning libraries are important in determining the optimum peptide sequence. It substitutes the amino acid(s) at positions of interest with all other natural amino acids sequentially. Using this methodology, it is possible to generate a more active peptide by identifying potentially more favourable residues for a given position.

Truncated peptide libraries

Truncated peptide libraries allow researchers to determine the minimum length of a peptide that is required for epitope activity. The original peptide sequence is systematically truncated, and each resulting peptide can then be tested. For long peptides, this can be used in conjunction with Inert insertion scanning libraries.

Quality

All of our peptides are identified using MALDI mass spectrometry, on equipment calibrated using internal and external calibration standards. We provide mass spec data with each peptide as standard, and all purified peptides come with an analytical HPLC trace if required. We also offer:

- Liquid Chromatography-Mass Spectrometry
- Electrospray mass spectrometry
- Amino Acid Analysis/ Peptide Content Analysis
- N – C terminal sequencing
- Nuclear Magnetic Resonance (NMR) data
- Stability testing

Our analysis and QC suites are equipped with analytical HPLC systems for determining peptide purity, Matrix Assisted Laser Desorption Ionisation Mass Spectrometry (MALDI) for highly accurate determination of peptide identity, Electrospray Ionisation Mass Spectrometry for determination of small peptides and characterization of reagents, and Ultraviolet Spectrophotometers, as well as a range of other instrumentation.

Natural and un-natural modifications

At Pepceuticals we are able to modify peptides to incorporate a range of moieties or stereocentres, some of which are listed in the table below. Our staff is comprised of fully trained synthetic chemists, we are able to consider any chemically feasible adjustments to the peptide sequence.

N-Terminal	Internal	C-Terminal
Acetylation	Biotin	Amidation
Biotinylation	Dabcyl	Aldehydes
Cinnamoylation	Dabsyl	7-Methoxycoumarin
Dabcyl	Dansyl	Lysine[Biotin]
Dansyl	Fluorescein	Lysine[Fluorescein]
Dinitrophenyl	Dehydro amino acids	Pegylation
Fluorescein	Hydroxyproline	Rhodamine TAMRA
Fmoc	Citrulline	Chloromethylketone
Formyl	Homoarginine	p-nitroanilide
Myristoylation	Lysine[Me]	N-methylamide
N-methyl	Lysine[Me ₂]	Monomethylarginine
Palmitoylation	Lysine[Me ₃]	Dimethylarginine (SDMA/ ADMA)
Steroylation	Arginine[Me]	Peptide nucleic acid (PNA)
7-Methoxycoumarin	Aminohexanoyl	
FITC	Reduced bond	
KLH	¹⁵ N labelled	
Pyroglutamoyl	¹³ C labelled	
BOC	Aminohexanoic acid	

This list of modifications is not exhaustive; please enquire if you have a specific modification.

Mass Spectrometry - Techniques for determining the molecular weight of peptides

- Maldi - TOF
- Electrospray

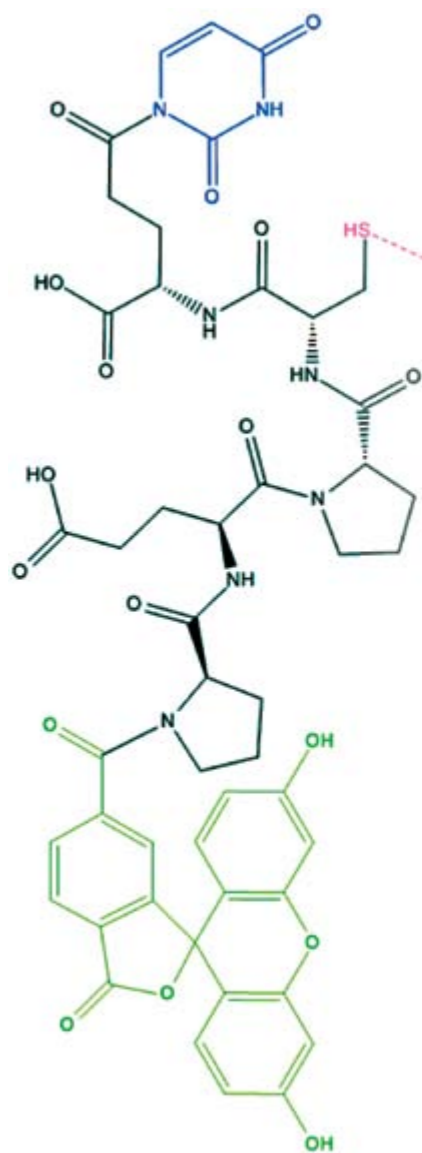
HPLC - Determines the UV purity of peptides

LCMS - This technique combines the power of HPLC and Mass Spectrometry

Amino Acid Analysis (AAA) / Peptide Content Analysis - Used to quantify the individual amino acids in a peptide

N / C - terminal sequencing - enables identification of the peptide sequence





Disulphide bridged peptides

We have considerable expertise in synthesising complex peptide molecules containing multiple site-specific disulphide bridges, and are able to adopt a range of methods in order to control the disulphide linkage.

Cyclic peptides

We are able to prepare cyclic peptides, cyclised from the N to C terminus, and have successfully synthesised a large range of cyclic peptides.

Phosphopeptides

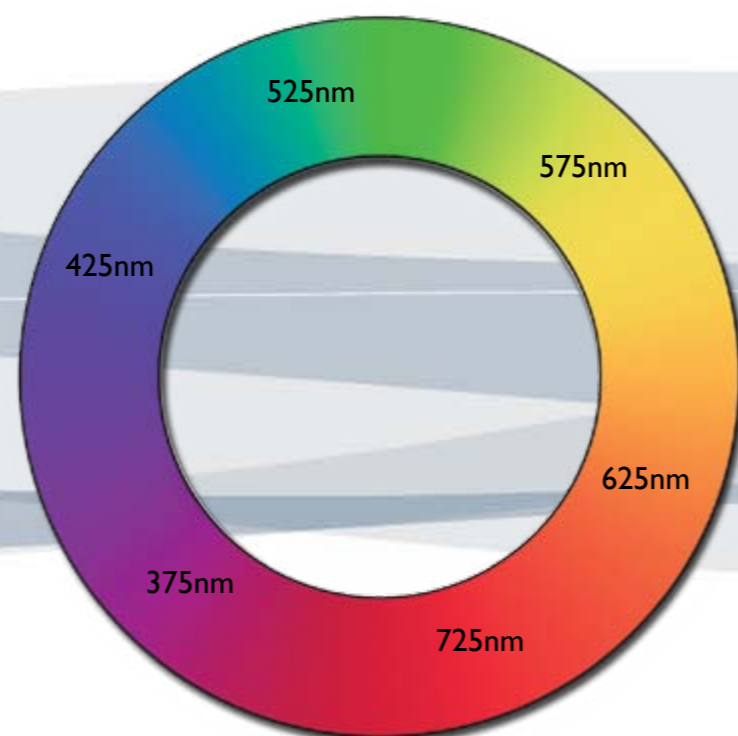
We have extensive experience in the synthesis and purification of multiple-phosphorylated peptide sequences, and their non-phosphorylated analogues. We routinely synthesise peptides containing one or two phospho groups, and have successfully synthesised high purity tri-phospho peptides, and other phospho-peptide molecules containing sequence modifications such as site specific chromogenic/ fluorogenic labeling.

We regularly prepare phospho-peptides for the generation of phospho-specific antibodies, and offer a complete anti-phospho-peptide antibody package.

Labelling - Chromogenic/ fluorogenic

Fluorescence/ chromogenic labelling is a very popular viable alternative to radiolabeling. The increased stability is a key benefit for using this type of labeling approach. Fluorescent and chromogenic groups can be easily attached to various functional groups, thus making them versatile tools for detection experiments. We have considerable experience in labelling technology, and have prepared peptides as complex as cysteine bridged phospho-peptides incorporating site specific labelling using two different dye molecules.

We are able to offer a wide range of labels, please enquire for further details.



Radiolabelling

At Pepceuticals we are able to provide a comprehensive radiolabeling service and would welcome the opportunity to discuss your radiolabelled peptide requirements. Pepceuticals offer custom synthesised radiolabelled peptides to suit your research needs at affordable prices. We routinely offer carbon (^{14}C), tritium (^3H) and iodine (^{125}I) radioisotopes to label peptides.

Pepceuticals routinely uses ^3H and ^{14}C for labelling peptides. The isotopes allow the labelling at high specific activities without compromising on the biological activity of the peptide.

The specific activity of tritium labelled peptides can be increased or decreased simply by increasing the number of tritium atoms per peptide molecule. A summary of different specific activities that can be achieved with some amino acids is shown in the table below.

	Maximum specific activity achievable
Proline	57Ci/mmol
Leucine	200Ci/mmol
Phenylalanine	285Ci/mmol
Tyrosine	57Ci/mmol
Alanine	57Ci/mmol

Higher specific activities can be achieved by labelling multiple amino acids within a peptide. Conversely, the specific activity of the labelled peptide can be reduced to any desired value by diluting the material with unlabelled material.

Labelling position: At Pepceuticals we routinely offer a variety of tritium labelling services: catalytic reduction using

tritium gas, reduction with sodium borohydride (^3H), reduction with lithium aluminium hydride (^3H), tritium gas exposure labelling service, tritiated water exchange labelling services, N-methylation using methyl iodide (^3H), N-acetylation using N-acetoxyphthalimide (acetoxy- ^3H).

The easiest route to obtaining tritium labelled peptides involves the catalytic reduction of a peptide analogue/ precursor containing unsaturated amino acids, using tritium gas.

Amino Acid incorporated	Labelled Amino Acid	Specific Activity
3,4 - dehydropoline	3,4 H-proline	30-60Ci/mmol
4,5 - dehydroleucine	4,5 H-leucine	50-200Ci/mmol

All radiolabelled peptides are purified by reverse phase HPLC and each product is accompanied by a detailed analytical data sheet and HPLC chromatogram as well as a comparison to a cold reference standard.

All radiolabelled peptides are purified by reverse phase HPLC and each product is accompanied by a detailed analytical data sheet and HPLC chromatogram as well as a comparison to a cold reference standard.

Stable isotope labeling

We are able to synthesise peptides incorporating stable isotope labelled amino acids, such as ^{13}C , ^{15}N and ^2H . This labeling technique is useful for studying peptides in solution using NMR spectroscopy. We welcome the opportunity to discuss your research requirements.

Catalogue Peptides



We hold a catalogue of over 4000 peptide entries covering a wide range of research areas, that include:

A	E	Neuromedins
Acetalins	Endomorphins	Neuropeptide Y and related Peptides
ACTH and Related Peptides	Endorphin Peptides	Neuropeptides
Adipokinetic Hormones	Endothelin & Related Peptides	Neurotensins and related Peptides
Adjuvant Peptides	Enkephalin & Related Peptides	NF-kB/Transcription Factors Related Peptides
ADP-Ribosylation Factors (ARF)	Enzyme Substrates and Inhibitors	Nociceptin, Nocistatin & Related Peptides
Adrenomedullins	Exendins	O
Adrenocorticotrophic Hormone (ACTH) Peptides	F	Orexins
Agouti Related Peptides	FDC-SP Related Peptides	Osteocalcin Fragments
Allatostatins	Fibrinogen and Related Peptides	OVA Peptides
Amylin Peptides	Fibronectin & Related Peptides	Oxytocin & Related Peptides
Amyloid Peptides	FRET Peptides	P
Angiotensins and Related Peptides	G	Pancreatic Polypeptides
Annexin	Galanin Peptides	Parathyroid Hormone (PTH) & Related Peptides
Anti-Inflammatory Peptides	Gastric Inhibitory Peptides (GIPs)	Peptide Standards
Antimicrobial and Related Peptides	Gastrin Peptides	Peptide YY & Related Peptides
Antioxidants	Ghrelin Peptides	Peptidoglycan Peptides
Apelin Peptides	Glucagon Peptides	Phosphopeptides
Arg-Phe-Amide RFamide Related Peptides	Glucagon-Like Peptides	Phytochelatins
Atrial Natriuretic Peptides (ANP)	Growth Factor Peptides	Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) Peptides
B	Growth Hormone Related Peptides	Prion Protein Peptides
Bacterial Peptides	Guanylin Peptides	Proactin Releasing Peptides
BAD Peptides	H	Protease Activated Receptor (PAR) Peptides
Bag Cell Peptides	Heat Shock Proteins	Protease Inhibitors
BAM (Bovine Adrenal Medulla) Peptides	Hepatitis C Virus (HCV) Related Peptides	Protein Kinase & Related Peptides
Basic Fibroblast Growth Factor (bFGF)	High Mobility Group (HMG) Peptide	Protein Phosphorylation Related Peptides
Bombesin Peptides	Human Immunodeficiency Virus (HIV) & Related Peptides	Proteolipid Proteins
Bradykinin & Related Peptides	I	S
Brain Natriuretic Peptides (BNP)	Integrin Peptides	Saposin Related Peptides
C	K	Secretin Peptides
C3a Peptides	Kinases/ Phosphatase Substrates	Selectin Related Peptides
Calcitonin & Calcitonin Gene Related Peptides (CGRP)	L	Signal Transduction Peptides
Cancer Research Peptides	Leptin Peptides	Somatostatin & Related Peptides
CART (Cocaine- and Amphetamine-Regulated Transcript) Peptides	Luteinizing Hormone Releasing Hormone (LHRH) Peptides	Substance P & Related Peptides
Casmorphan Peptides	M	T
Caspase Related Peptides	Mast Cell Peptides	Tachykinin Related Peptides
Cecropin Peptides	Mastoparan Peptides	Tag Peptides
CEF Control Peptides	Matrix Metalloproteinases (MMPs)	Thrombin & Related Peptides
Cell Permeable/Drug Delivery Peptides	Melan-A and Mucin Related Peptides	Thrombospondins
Cholecystokinin Peptides (CCK)	Melanin Concentrating Hormone (MCH) & Related Peptides	Thyrotropin Releasing Hormone (TRH) & Related Peptides
Cholecystokinin-Pancreozymin Peptides	Melanocyte Stimulating Hormone (MSH) & Related Peptides	Toxin Peptides
Corticotropin Related Peptides	MHC related Peptides	Tumour Necrosis Factor (TNF) & Related Peptides
Corticotropin Releasing Factor (CRF, CRH) & Related Peptides	Microbial Peptides	U
C-Peptides	Miscellaneous Peptides	Urocortin & Urotensin related Peptides
Cytochromes and Related Peptides	Myelin Peptides	V
D	N	Vasoactive Intestinal Peptide (VIP) & Related Peptides
Defensins	Natriuretic Peptides	Vasopressin & Related Peptides
Dermorphin Peptides	Neurokinins	Viral Peptides
Dynorphin Peptides		X - Xenopsin & Related Peptides

Peptide synthesis reagents and resins

We stock a wide range of peptide synthesis reagents and resins, all of which have full trackability, and are supplied with a Certificate of Analysis. Please browse our catalogue for our listings.

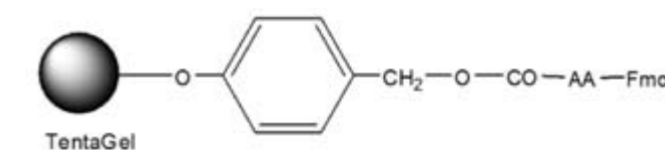
Amino acids

Fmoc protected amino acids

Fmoc chemistry peptide synthesis is based on an orthogonal protecting group approach. It uses the N-Fmoc group to protect the alpha amino group, which can be readily deprotected for subsequent use in acylation reactions. The extent of deprotection can be monitored by UV spectroscopy, as the by-product of the reaction has a large chromophore.

Resins

Resins play an important role in modern peptide synthesis helping facilitate cleaner reactions, improving reaction times and ensuring that the final product is easier to isolate. At Pepceuticals, we offer a wide range of resins for solid phase peptide synthesis which are sold preloaded with the first amino acid group attached. A Certificate of Analysis accompanies the resin, which contains details of the amino acid loading.



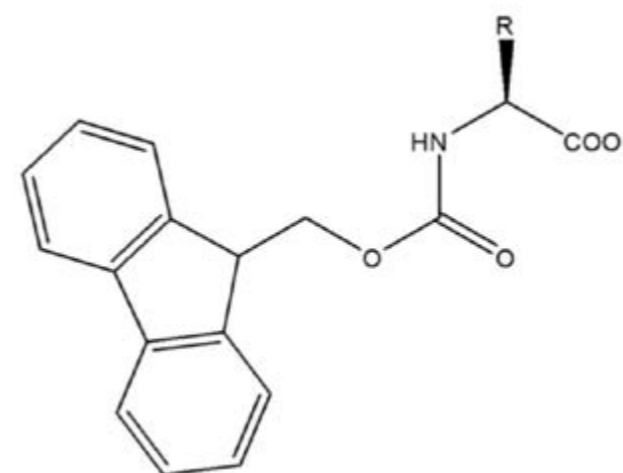
TentaGel

TentaGel resins have good swelling properties, ensuring high solvation characteristics and exhibiting reduced aggregation during peptide assembly. These excellent swelling properties are maintained with a broad range of usable solvents. TentaGel resins can be utilized in almost all solvent systems. TentaGel resins are more stable under higher pressures and can therefore be used in continuous flow synthesis as well as batch synthesis.

TentaGel S resins are the standard type of resin used for peptide synthesis, solid phase organic synthesis and combinational chemistry. TentaGel R resins exhibit increased swelling volume and lower pressure resistance making them ideal supports for large peptides and difficult sequences.

Chlorotriyl polystyrene

These resins are mainly used in batch synthesis, however they can be used in continuous flow if the resin beads are co-packed with glass beads, or if low flow rates are used. Chlorotriyl resins can also be used in fragment condensation reactions when dealing with difficult peptide sequences.



Boc protected amino acids

Boc chemistry is more favourable for complex synthesis involving base-sensitive non-natural peptide analogues as it employs harsher conditions.

Coupling reagents and additives

Amide bond formation methods employed in organic synthesis are generally regarded as too harsh for peptide synthesis. Milder activating methods have therefore been sought. Uronium based chemistry provides an excellent methodology for peptide synthesis. HCTU is commonly employed as a coupling reagent, however we also provide a number of other uronium based reagents including HBTU, HCTU, HATU, TBTU, TCTU and TNTU.

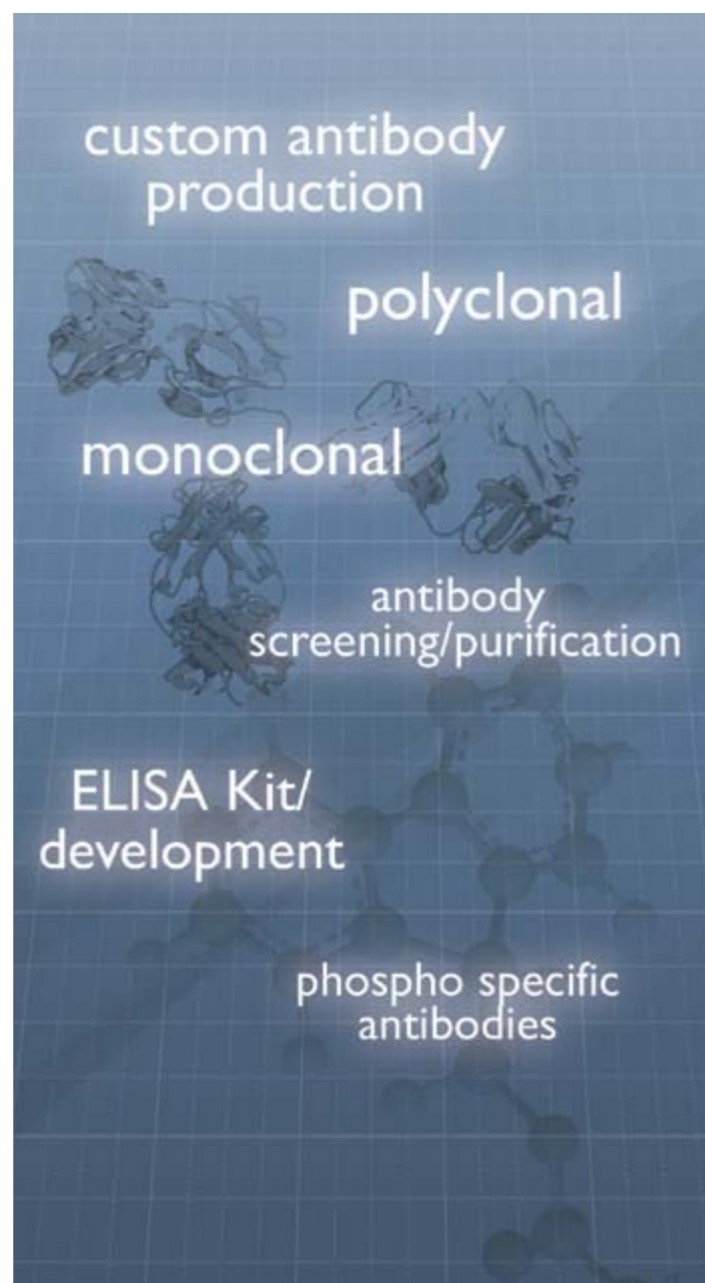
We can provide a range of additives including HOBt and chloro-HOBt which are employed to minimise enantiomerisation during peptide bond formation.

Antibodies

Pepceuticals offer a fast, reliable and flexible service for polyclonal anti-peptide antibodies, from peptides synthesis through to ELISA titration and serum delivery. Our flexibility allows us to tailor the preparation to your needs.

We have been supplying antibodies since 1998, and use high quality antigens in conjunction with a reliable immunisation schedule, in order to raise the most mature antibodies.

Our antibody packages are flexible in order to allow the customer to receive the service that is best tailored to their needs. If required, we are able to undertake antibody projects in which the antigen is supplied to us. We will require 2-5 mg of the antigen, at a concentration of 2-3 mg/mL.



Antigen selection

We are able to advise on potential antigen candidates from a peptide/ protein sequence, should this be required. Our scientists use modern qualified methods for determining regions of a sequence that are suitable for use as an antigen candidate.

The smallest synthetic peptides that will consistently elude antibodies that bind to the original protein are 6 amino acids long. Smaller peptides often lead to weak or no immunogenic response. Generally peptides should be of minimum length 10 amino acids.

Antigenic response to most peptides can be induced successfully by careful synthesis, coupling and immunisation, leading to specific antibodies. What most researchers want to know is how likely will it be that anti-peptide antibodies will recognise the native protein?

Suggestions for choosing the peptide sequences would be: If possible select more than one peptide sequence from the native protein.

- Use the carboxy terminal sequence if it is hydrophilic and a suitable coupling group is available or can be added.
- Use the amino terminal sequence if it is hydrophilic and a suitable coupling group is available or can be added.
- Use internal hydrophilic regions that are perhaps longer in peptide length.

Screening

All anti-sera produced are cross reacted with the unconjugated peptide using an optimised ELISA titration system. The data obtained will be supplied upon completion of the project, along with the antisera, and a reference sample of the unconjugated peptide antigen. We are able to provide pre-screening data on projects if required.

Peptide synthesis:

Upon receipt of the antigen candidate sequence, our peptide synthesis chemists design the best synthetic route to the peptide target molecule, incorporating a Cysteine residue for use in conjugating the peptide to a protein carrier where required. Using either automated or manual synthesis, the peptide is prepared and purified as required to the appropriate quality. The integrity of the sample is checked prior to the conjugation to a protein carrier, and a sample of the peptide reserved as a reference standard.

Purification

We are able to offer purification of crude antisera by Affinity purification, protein A or G purification. This gives highly specific antibodies from the antibody pool, and is used in the preparation of phospho-, and acetylation-specific antibodies.

Phospho-specific antibodies

We have a wealth of experience in raising phospho-specific antibodies. We ensure that the peptide antigens used are of the highest quality in order to provide the most active, specific antibodies possible. By utilising affinity purification, antibodies are isolated which specifically recognise the phosphorylated antigen, and not the non-phosphorylated antigen.

Protein carriers

An important factor when designing synthetic peptides for use in antibody production is the method used to couple the peptide sequence to a protein carrier. Most coupling methods rely on the presence of free amino groups, found in lysine side chains or on amino-terminal residue, sulfhydryl groups found on cysteine, phenolic groups found on tyrosine, carboxylic acid groups found on aspartic acid, glutamic acid and the carboxy terminal residue.

The easiest strategy to manipulate the type of coupling is to add an extra amino acid on either the amino or carboxy terminus to allow simple one-site coupling to the carrier.

Many different carrier proteins can be used for coupling with synthetic peptides. The two most commonly used are KLH and BSA. For most purposes, either carrier will be adequate. At Pepceuticals we can employ other carriers of choice (i.e. ovalbumin, MSA, RSA).

Antigenicity of material

The success of a custom hybridoma project is dependent upon the antigenicity of the material supplied by the client. Pepceuticals cannot guarantee that the material supplied by the sponsor will produce an immune response sufficient to warrant continuation of the mab protocol. Pepceuticals guarantees that the antibodies produced by hybridomas developed will recognise the immunogen as assayed by ELISA. The sponsor is responsible for determining the utility of these antibodies in their specific applications. All resulting hybridomas, their antibodies, and reagents supplied are solely the property of the client. At the completion of the project, these items will be returned to the client.

Additional services

Cryopreservation/ storage of two clones from each parental culture for six months is included in the monoclonal antibody package, however this can be extended if required. Please enquire for further information.

We are also able to offer ascites production, elisa kit development, and affinity purification. Please enquire for details.

Monoclonal Antibodies

Working to the sponsors specific requirements, Pepceuticals hybridoma production service will undertake the isolation and development of murine hybridomas secreting monoclonal antibodies reactive to the antigen (synthetic or non-synthetic protein) of choice.

Although programmes may vary, the standard procedure involving three phases will typically take 4-6 months to complete.

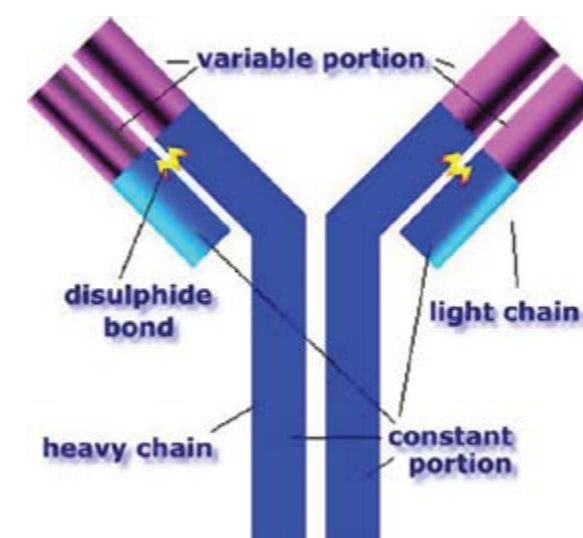
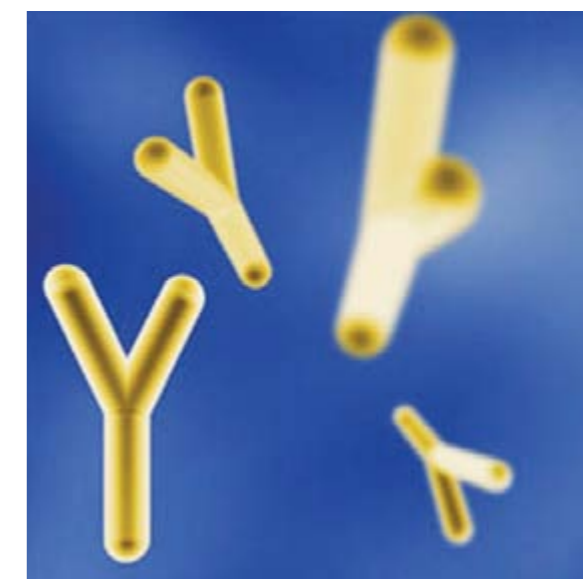
Procedure	Day	Description
Antigen Preparation	Day 0	Synthesis of peptide, purification and conjugation
Control Serum Collection	Day 0	Tail vein bleeds taken prior to start of immunisation (pre-immune bleed)
1st Injection	Day 1	Intraperitoneal injection of 10-50µg of purified peptide or protein coupled to KLH (complete Freund's adjuvant)
2nd Injection	Day 21	Intraperitoneal injection of 10-50µg of purified peptide or protein coupled to KLH (incomplete Freund's adjuvant)
3rd Injection	Day 42	Intraperitoneal injection of 10-50µg of purified peptide or protein coupled to KLH (incomplete Freund's adjuvant)
4th Injection	Day 45	Intraperitoneal injection of 10-50µg of purified peptide or protein coupled to KLH (in PBS)
5th Injection	Day 46	Intraperitoneal injection of 10-50 µg of purified peptide or protein coupled to KLH (in PBS)
Isolation of Hybridoma	Day 50	Isolation by cell fusion with a non-secreting myeloma cell line
Incubation	Day 50	Hybridomas will be incubated for at least two weeks following cell fusion.
ELISA 1	Day 64	Verify disposition of host
ELISA 2	Day 71	Re-verify disposition of host
Cryopreservation of 2 clones	Day 71	Cloning of important parental cell lines, storage for 6 months and provision of 50ml of each antibody supernatant for client use

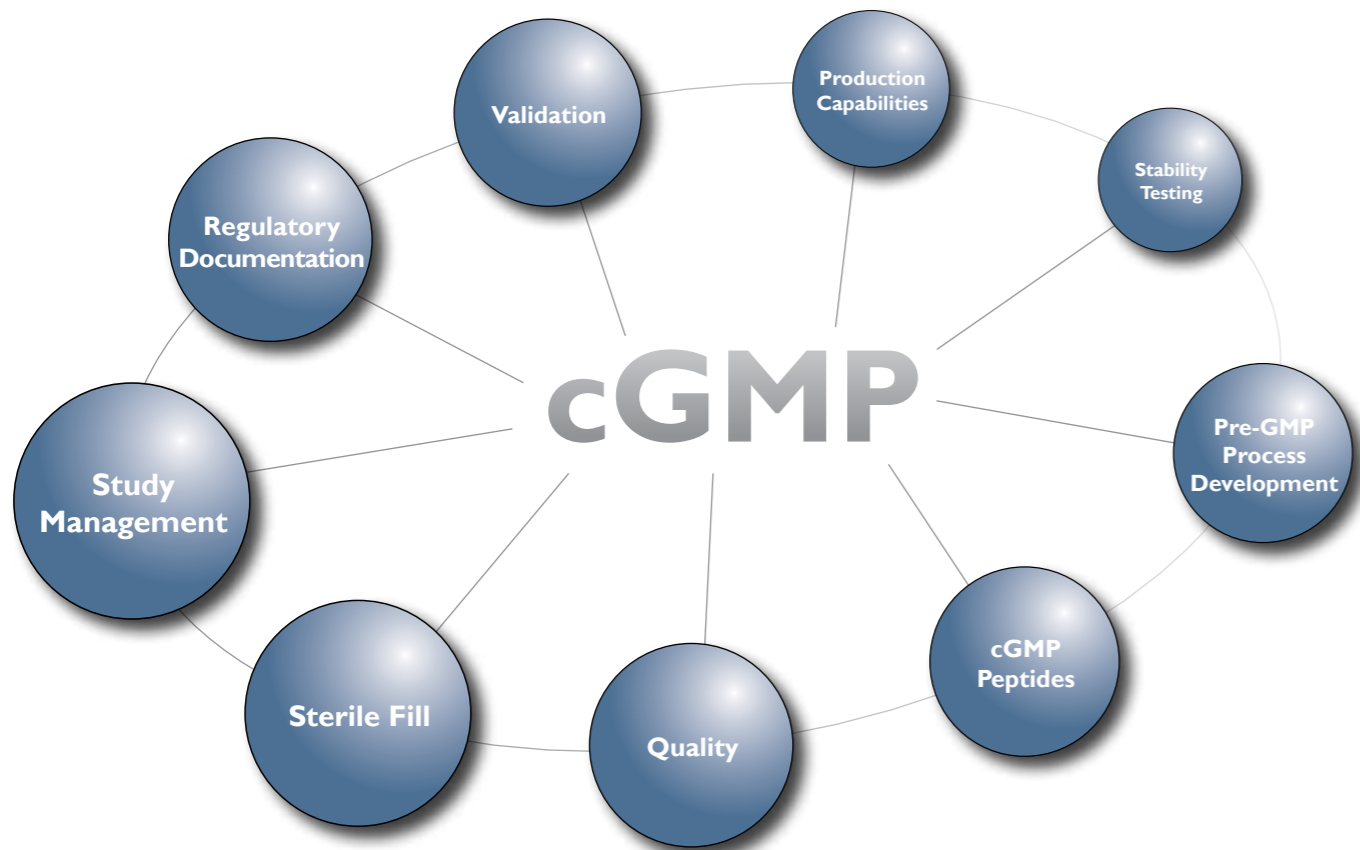
Polyclonal Antibodies

Our standard protocol is based on two rabbit hosts per immunisation programme, however we do offer other species on request, please enquire for further details. We can also offer a pre-screening service for where cross reactivity may be an issue, in localisation studies for example.

Procedure	Day	Description
Antigen Preparation		Synthesis, purification and conjugation of the peptide
Control Serum Collection	Day 0	Immunisation of host
1st Boost	Day 14	Antigen boost
Serum Collection	Day 28	
2nd Boost	Day 42	Antigen boost
Serum Collection	Day 56	
3rd Boost	Day 56	Antigen boost
Serum Collection	Day 70	Production bleeds
Purification of antibodies if required		Antibody affinity purification if required
Shipping to customer		Peptide sample, antibodies and documentation

The schedule can be tailored to suit individual requirements, and a continuation of the project is offered on a month-to-month basis. The extension protocol includes one boost, serum collection and maintenance for one month.





cGMP

Pepceuticals offers a versatile cGMP service to support research and in-process projects from pre-clinical toxicology studies through to early stage clinical trials. We help our customers reduce the discovery-to-market timeline by providing development to medium-scale manufacturing at one facility. We provide CMO and CMR services for the manufacture of active substances including peptides.

- Pre-GMP process development and process transfer
- Re-processing or finishing of existing materials (sterile fill)
- Preparation of reference standards
- Analytical method development and validation
- API manufacture
- Stability testing
- Process validation
- Support with regulatory documentation



Our facility which is based in Leicestershire (UK), houses over 10,000 square feet of modern laboratories which incorporates eight cGMP suites. The facility has been designed and built to meet national and international standards (EC guidance for GMP, Eudralex Vol. 4, Part I, II and Annex I; ICH Q7A; US Federal Standard 209 E; and the ISO classification) required for API manufacture.

Designed specifically for versatility, the access-controlled facility operates at a minimum of Grade C (Class 10,000; M 5.5; ISO 7), encompassing Grade B laboratories incorporating a laminar flow Grade A (Class 100; M 3.5; ISO 5) cabinet. Offering a selection of large and medium sized cGMP laboratories equipped with built-in fume cupboards and walk-in fume cupboards, our state-of-the-art facility and highly trained scientists ensure that your project requirements are exceeded.

Production capabilities

Our facility and extensive experience in cGMP enable us to offer a complete solution for your project requirements, including:

- Study management – a dedicated Study Manager will liaise with you regarding the progression of the project
- Process research and development, including process transfer – scientists working on your project will assess and improve the manufacturing process
- Analytical method development and validation – dedicated analytical scientists will optimise procedures in order to accurately identify API and related substances
- API manufacture – production scientists will manufacture the active substance to support your study, in up to multi-kg quantities

- Aseptic processing including sterile filling
- Stability testing – evaluation of active substance under a variety of environmental factors such as light, temperature and humidity.
- Cold storage
- Lyophilisation

Stability testing

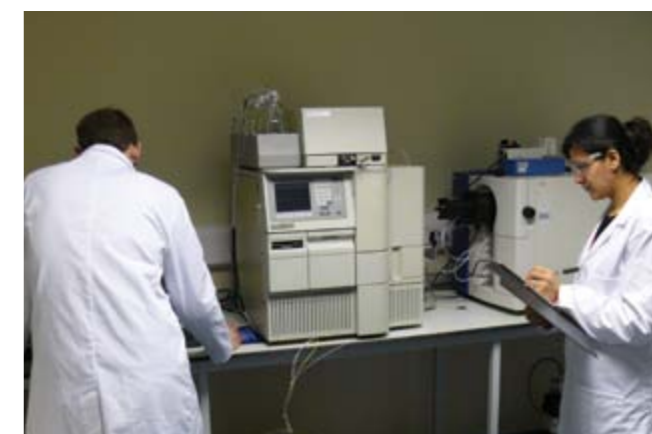
We are able to design, manage and conduct stability testing in order to support regulatory submission.

- Develop methods to test active substance stability
- Analytical testing of active substance
- Observe effects of environmental factors: Light, temperature and humidity
- Statistical analysis of results
- Evaluate storage solutions for active substance

Pre-GMP process development

Our team of experienced scientists will work to provide the most economic, environmentally benign and scalable synthetic route to the active substance.

- Yield optimisation
- Impurity identification and tracking
- Safety and environmental assessment of process
- Economic evaluation
- Feasibility study of alternative route(s)
- Process suitable for transfer to larger scale
- Identify and validate starting material suppliers
- Determine tolerance limits for processing parameters
- Identify storage conditions



Quality

We operate a BSI accredited ISO9001: 2008 UKAS Quality Management System (Certificate: FM 560179). Our Quality Manager oversees all aspects of Quality Assurance including the release of starting materials, documents and labels, audit of training, procedures and processes, final product release, and audits by regulatory bodies and customers.

Operating independently from production, the QC department evaluates the integrity of the active substance.

- Wealth of experience in analytical techniques
- Development and validation of analytical procedures
- Control and release of retention samples and standards
- Analysis of starting materials, including primary and secondary packaging
- Continuous monitoring of the cGMP facility and storages
- In-process and batch analysis
- Final product analysis
- Fully compliant ICH stability studies
- Equipment qualification

Critical analyses are undertaken using validated external procedures.



Sterile Fill

Our sterile fill capabilities include:

- Aseptic processing
- Terminal sterilisation by filtration
- Aseptic liquid and powder filling of vials, bottles, syringes and ampoules



All of our aseptic connections are made within a Grade A/ B environment.

Study Management

Each study has a dedicated Study Manager who is responsible for the Study Management Team. The team is committed to ensuring complete customer satisfaction. The Study Manager will act as a single point of contact for the customer, whilst the team will:

- Provide a Technical Agreement
- Project manage the research, method development and process transfer functions
- Provide a Quality Risk Assessment for the project
- Ensure all necessary qualifications and validations are completed
- Oversee all aspects of the manufacturing process
- Resolve issues that arise during the project
- Handle customer enquiries and provide progress reports
- Be responsible for product security, storage and 'chain of custody'
- Provide support for IND submission

Regulatory Documentation

For API manufacture we can supply the necessary documentation required for your project, or use existing documents as required. We are able to provide support with IND drug submission portfolios.

- SOPs for equipment usage, processes and activities
- Staff training records
- Certificate of Analysis for starting materials
- Technical agreements
- Production batch cards
- Certificate of Analysis for active substance

Validation

Project validation is assessed using Quality Risk Assessment strategies in order to determine critical stages in the process and



analysis. Equipment used within a critical stage is qualified before validations are undertaken. The scope and level of process validation will depend upon the number of batches of materials to be manufactured.

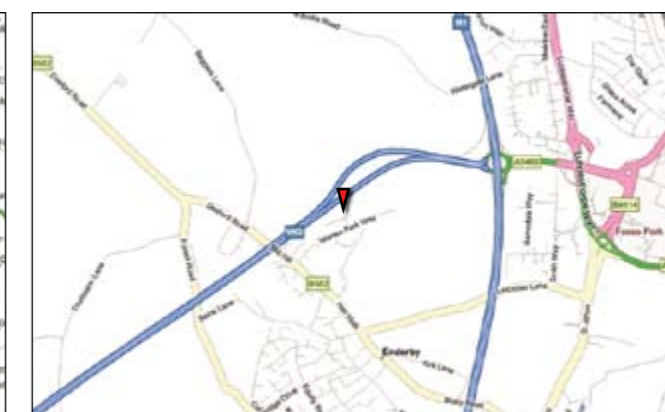
cGMP peptides

With the increasing focus on peptide therapeutic agents for healthcare, we aim to offer a complete solution to the pharmaceutical industry, by supplying peptides for pre-GMP research studies through to cGMP grade peptides.

With 13 years commercial experience in peptide synthesis, and over 40 years expertise in synthetic chemistry we are the ideal partner for your cGMP peptide requirements.

Our cGMP peptide services include:

- Peptides up to 130 amino acids in length
- Milligram to kilogram scale
- Chemically modified peptides
- Solid phase synthesis; using Fmoc or Boc methodology, suitable for most peptide sequences
- Solution phase synthesis – suitable for short peptides
- Fragment condensation technologies – for long peptide structures
- Large scale purification – Preparative reverse-phase HPLC, ion exchange chromatography and size exclusion chromatography
- Lyophilisation
- Peptide analysis



Contact Details

Our customer service and scientific support teams are available to assist with your enquiries between 9am and 5.30pm Monday to Friday.

We will be happy to prepare detailed quotations on request; please do not hesitate to get in touch with us using the contact details opposite.

Pepceuticals Ltd

4 Feldspar Close
Warrens Park
Enderby
Leicestershire
LE19 4JS

Tel: +44 (0) 116 284 9301

Fax: +44 (0) 116 286 2464

Website: www.pepceuticals.co.uk

Email: peptides@pepceuticals.co.uk

Feedback: feedback@pepceuticals.co.uk



Certificate No. FM 560179