Tepnel
Pharma Services

Enhanced Approach to Method Development Meets Regulatory Expectations and Provides Added-Value to Clients

Tepnel Pharma Services, UK

At Tepnel, our adoption of AQbD concepts and investment in state-of-the-art analytical equipment and software has helped us to modernise our approach to analytical method development. With fit-for-purpose, fully integrated hardware and software and highly skilled chemists we have been able to reduce turn-around times for method development from start to finish by around 30-50%, depending on the analytical complexity required.

Our streamlined approach brings benefit to our clients since we deliver better results in a shorter timeframe and helps Tepnel in terms of reduced costs and improved profitability. The ability to more accurately predict the time required to complete method development projects significantly helps in planning and costing statements of work.

Tepnel Pharma Services have invested in Waters ACQUITY UPLC method development system with Empower 3 CDS and S-Matrix Fusion QbD software. This integrated solution for robust method development has reduced method development turnaround times by ca 30-50%.

About Tepnel

Tepnel Pharma Services Limited (Livingston, UK) provides pharmaceutical testing in support of drug development with an emphasis on inhalation, oral dosage, parenteral and peptides/proteins. Tepnel provides CMC services for chemistry and microbiology for both small and large molecules, providing support from preclinical enabling stability and formulation selection through to batch release testing for the marketplace. With over 40 years of experience (founded in 1972), our staff are committed to providing laboratory services that deliver on the promise of accountability, affordability, and adaptability.

Tepnel provides the following services:

- Method Development & Validation to ICH requirements for APIs, Finished Products and Cleaning Validations (required to support the manufacturing process)
- Peptide, Antibody & Protein assays (ELISA, SDS Page, Western Blotting, UPLC-MS etc..)
- R&D support other than regulatory submission requirements to support the manufacturing process
- Handling capability for up to OEB4 potency compounds & controlled drugs
- Forced degradation studies – exposure to elevated temperatures, freeze/thawing, mechanical stress, oxidation, light etc.
- Stability Testing to ICH guidelines across the range of Climatic Zones including ASAPprime (Accelerated Stability Assessment Program for excipient compatibility studies)
- Technical Transfer/Method Transfer/Method Verification
- Quality Control –The pharmacopoeia chemistry and microbiology analysis required for APIs, raw materials, excipients and finished products
- Batch release testing

Method Development Services at Tepnel

An enhanced approach to analytical procedures, as described in the proposed ICH Q14 guidance, requires the application of risk-based methodologies to understand and measure sources of variability affecting the reportable results of a procedure. The recommendation is to apply quality by design principles when developing a method and to define the design space for the method within which assurance of quality is provided. The enhanced approach helps to increase method robustness and understanding and also leads to higher success rates when methods are transferred and verified.

Tepnel were one of the first companies to adopt Waters ACQUITY UPLC when this disruptive technology was first introduced and since then we have continued to invest in state-of-the-art equipment. The second generation UPLC, the ACQUITY UPLC H-Class is a low dispersion quaternary system with flexible column management options, supporting up to 6 columns on 5µm to sub 2µm chemistries, multiple solvent lines and is compatible with an extensive range of detectors. At Tepnel we require this flexibility to facilitate multiple column screening and detection of a wide range of compounds. Our Empower 3 CDS has a two-way data link with Fusion QbD method development software, facilitating fast data transfer and reducing transcription errors.

Fusion QbD software makes predictions based on empirical models generated from multi-variate experimental raw data and can be applied to both biologicals and small molecules. This software is extremely useful in terms of shortening the method development phase and identifying critical parameters and optimal method performance can be achieved far more rapidly than through traditional linear trial and error, or best guess approaches.

The adoption of modern AQbD concepts in conjunction with our in-house separations expertise and the use of fit-for-purpose analytical technology facilitates faster and better method design and development, which in turn is reflected in the cost and time to market the product. The submission of design space information is also looked upon very favourably by the regulators.

Approaching challenging peptide separations

In recent times, Tepnel has been challenged to design methods to analyse a number of extremely complex mixtures of peptides. In many cases, methods were either non-existent and required full development or were not fit-for-purpose having been developed for research purposes and needed re-evaluation and development before verification and validation to GMP/ICH requirements.

In addition, peptides are notoriously difficult to separate due to their physical and chemical characteristics, the molecular size, charge, polarity, solubility (once out of solution they may not redissolve due to being denatured) and specific covalent or non-covalent interactions causing dimerism. Additionally, the charge state of a peptide may be altered by a change in the pH, which will affect some or all of the preceding characteristics.

Here we present two case studies, describing Tepnel's approach to the development of new methods for this challenging class of molecules.

Case Study 1

Our client was developing a novel peptide drug product and required quality control analytics of the API's to be used for manufacture. We were trusted to develop a novel method for determination of peptide purity to be used for batch release and stability.

The development was completed within a design protocol to build quality and reliability into the development activities and included the following goals:

- Utilise high resolution, low dispersion LC technology
- Primary detection source to be UV but the method must be MS compatible
- Separation of critical peaks must be obtained
- Reduce run time and improve sensitivity
- Automated scouting/screening using Acquity H-Class combined with UV and MS detection
- The method identified was to be optimised and validated.

The benefit of using our method development approach:

- Increased efficiency from a reduced run time
- Increased separation, resolving power of method increased by 5 times
- Increased sensitivity of the method delivering 10 times more sensitivity to detecting impurity peaks
- Typically, >90% purity claimed; Actually 60-70% found
- Redevelopment brought advantages of cost and time saving coupled with confidence and accuracy in the data produced
- Method robustness displayed with adoption for long term stability projects
- Method finally used for regulatory submission

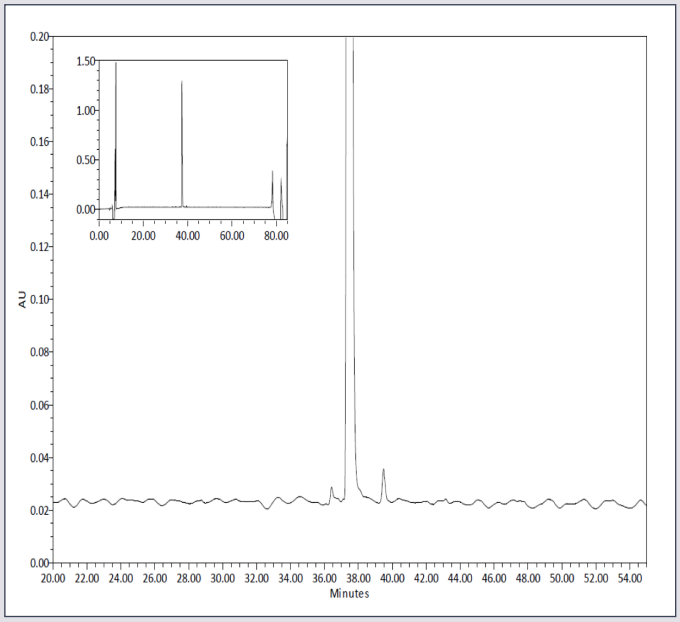

Fig. 1. Pre-optimisation Chromatogram

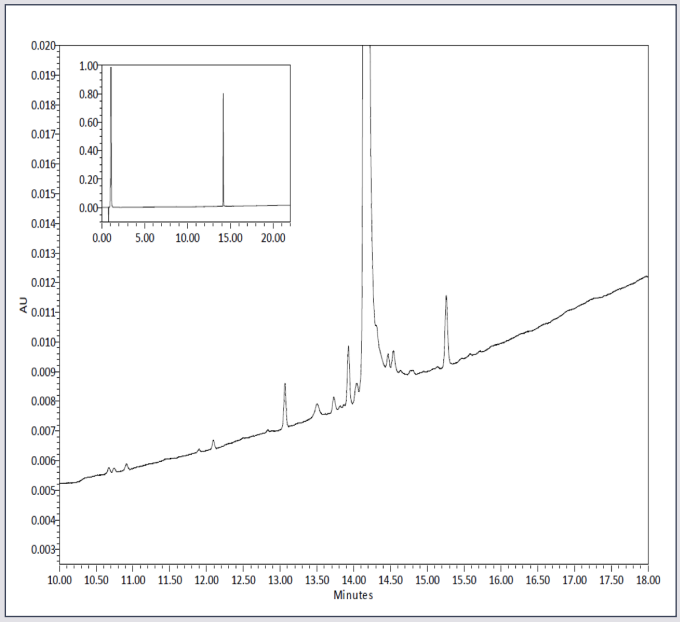

Fig 2. Post Optimisation Chromatogram

Case Study 2

Development of a peptide aggregation method for a combined peptide drug product. We were trusted to re-develop a method for determination of peptide aggregation to be used for peptide product batch release and stability. Existing HPLC-UV methodology was available, but this had the disadvantages of:

- Not being MS compatible
- Time consuming with a 40 mins run time
- Poor separation resulting in poor specificity
- The method could not identify dimers or aggregates accurately

Using our method development approach we were able to successfully build quality and reliability into the development activities, based on the following goals:

- Utilise UPLC technology
- MS compatible
- Decrease run time to improve efficiency and improve sensitivity and separation to increase specificity

The benefits of new the methodology were:

- Reduced run time (x3 increase in efficiency)
- The SEC-MS method developed allowed identification of eluting peaks coupled with UV detection for quantitation thus increasing specificity
- Increased separation, resolving power of method was increased by 5 times.
- Increased sensitivity, the method was 10 more sensitive to detecting impurity peaks.
- Redevelopment brought advantages of cost and time saving coupled with confidence and accuracy in the data produced.

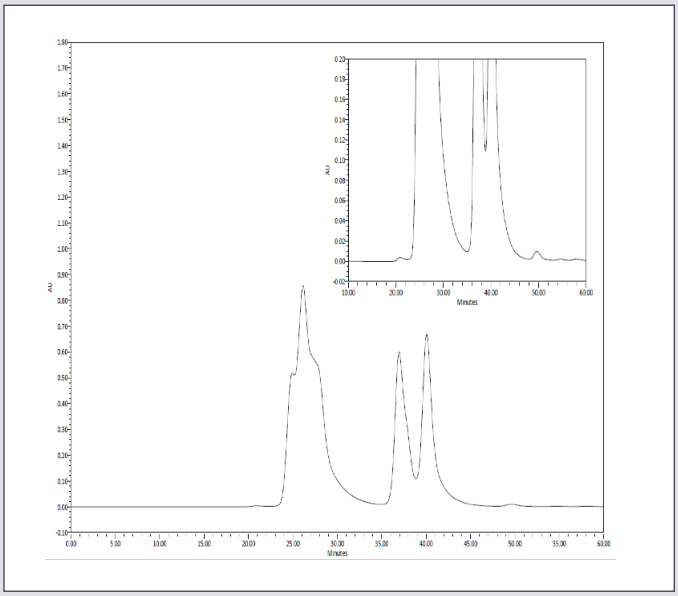

Fig. 3. Pre-optimisation Chromatogram

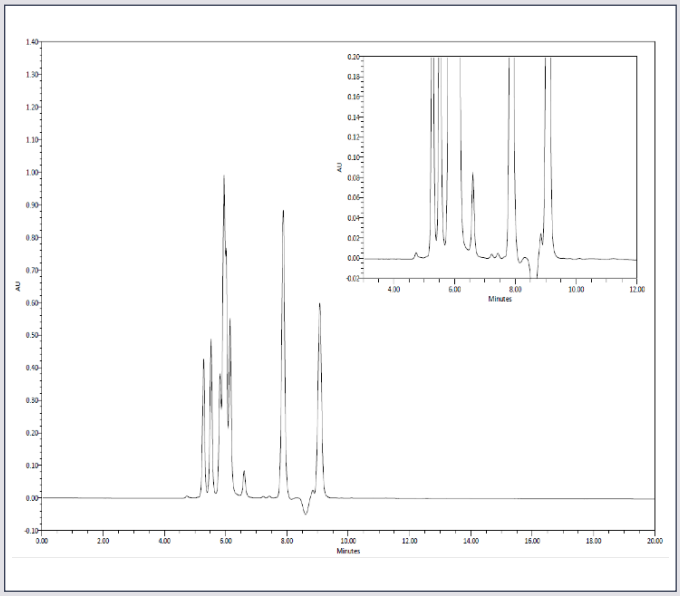

Fig. 4. Post Optimisation Chromatogram

Benefits to Our Customers

- Shortening of the method development phase with associated lower costs and time to market
- The future proofing of methodology to ensure a method works first time in a robust manner
- The method critical process parameters are controlled within the system suitability set up, which allows for easier transfer of the validated method

To find out how partnering with Tepnel can reduce cost and accelerate your drug development programme please contact:

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Reference: 1. ICH Topic Q 2 (R1) Validation of Analytical Procedures June 1995