Probing Deep Understanding of an LC-UV-MS Method for Characterising Oligonucleotides

Challenge

Britest

Method development to deliver a simplified platform method for assay and impurities for oligonucleotides (an important emerging class of gene targeted therapeutics) is not straightforward.

The complexity of oligonucleotide structures and the large numbers of non-resolvable impurities and stereoisomers involved require both UV and MS dimensions for quantification in Liquid Chromatography (LC). The method involves multi-step manual data processing and subjective interpretation by the analyst at some key stages. Thus detailed training is required to ensure analysts are competent, both in-house and at partner organisations.

In this case, the accelerated timelines for lead oligo drug product New Drug Application (NDA) filing did not allow for full development of a simplified method, so deep understanding of the existing method was required to drive method improvement and standardisation.

Approach

A facilitated Britest study was conducted, to identify opportunities to remove subjectivity from the method, which was believed to be leading to deviations, inconsistent results, and System Suitability Test (SST) failures.

Breaking the analytical method down into a flowchart, a tailored form of Britest Duty Definition and Equipment Specification (DuDES) analysis was used to develop a risk prioritisation and mitigation strategy for each task needed to analyse the drug product. By identifying what each task *must have or attain* and conversely *what must be avoided*, the project team were able to generate and discuss a set of potential actions to mitigate the risks identified.

Benefits

- · Harmonisation across departments and with external partners.
- Identification of actions to improve training materials and internal standardised method.
- A standardised method is beneficial for in-country testing, i.e., where drug product is tested by government labs without a formal test transfer.

DuDES is a promising technical deep dive tool to complement our existing risk assessments.

ANALYTICAL SCIENTIST, New Modalities and Parenteral Development

) is **Client -** Multinational pharmaceutical manufacturer Industry - Application Area

Key Features:

Pharmaceuticals - Analytical method improvement and standardisation, Operational excellence

Challenge

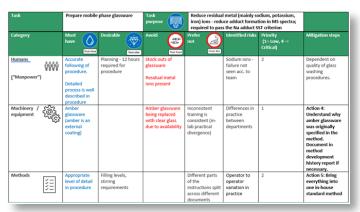
A simplified platform method for determining assay and impurities for oligonucleotides is desirable but the accelerated timelines for lead oligo drug product NDA filing did not allow for full development of a simplified method.

Solution

Deep understanding of the existing method can be used to inform improved training and method standardisation. The Britest methodology was used to complement established methods of Analytical Risk Assessment (ARA) in this respect.

Outcomes

A facilitated Britest study based on a tailored DuDES analysis identified opportunities to remove subjectivity from the method, leading to harmonisation across departments and external partners, identification of actions to improve training materials and the internal standardised method, and consequential benefits for in-country testing.



Extract from DuDES analysis focusing on mobile phase glassware preparation

Contact +44 (0)161 327 1579 enquiries@britest.co.uk www.britest.co.uk

Generating value from process understanding