The essential upgrade for modern pharmaceutical NMR

Recent conversations with a leading user of NMR – currently working on structural elucidation in the early development group of a major US-based pharmaceutical company – concentrated on the theme of contemporary developments in NMR.

With more than 25 years' experience in the lab, and a perspective gained from working in applications development and customer training for a major analytical instrument company, he offers a unique view on how modern NMR hardware platforms, probes and software stack up against industry needs for rapid, straightforward analysis of fluorine-containing drug candidates.

Challenges and trends in pharma NMR

Against a background where analysts in the pharmaceutical industry are increasingly looking for accurate, easy-to-use and scalable methods throughout the R&D, QC and drug manufacture pipeline, Nuclear Magnetic Resonance spectroscopy (NMR) has become established as a leading technique. NMR gives an unmatched breadth of information on the sample, including strikingly detailed structural elucidation. When properly implemented, the technique also offers straightforward method development, allows rapid throughput without destroying the samples used and, importantly, is a direct quantitative method with no requirement for response factors and calibration curves.

> **"Five years ago, we could see Fluorine coming; today – with more than 50% of the new compounds that come to me from discovery being fluorinated – it's in your face every day!"**

As regulators expect a company to know much more about their drug compounds – and to have this information early in the development process – NMR is now often used in parallel with Mass Spectrometry so that discovery and development scientists can access structural information and mass data at the same time.

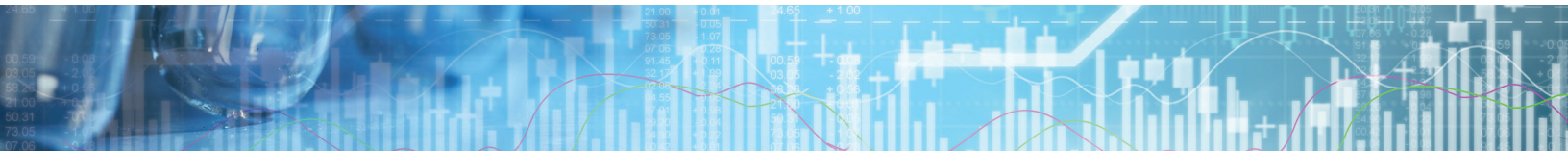
In recent times, Fluorine-containing compounds have become increasingly important. By 2011, more than 200 marketed medicines, and approximately one third of the most successful – so called, 'blockbuster' – drugs contained fluorine atoms in their structure[1].

Moreover, around 40% of small molecules entering advanced (phase III) clinical trials in 2012 and 2013 were fluoro-organic compounds[2].

Fluorine chemistry is used in a wide variety of drug applications, including: antibiotics, antacids, antibiotics, anti-depressants, antihistamines, Arthritis/anti-inflammatory agents and psychotropics, for example[3].

> **"We now have a hardware platform that allows us to do investigations that were never available before – and we have a library of well worked out experiments that just work right out of the box – so we are at the stage of exploring the new limits and defining best approaches..."**

Consequently, the spotlight has fallen on the techniques used for the analysis of fluorine-containing pharmaceutical substances – including active pharmaceutical ingredients, branded and generic finished products. Traditionally, NMR analysis is based on ^{13}C and ^{1}H, however, ^{19}F NMR of fluorine-containing compounds can be very useful because of much higher ^{19}F NMR sensitivity. ^{19}F also has less risk of signal overlap due to its broad response range, in comparison to ^{1}H. Moreover, ^{19}F NMR provides a wealth of detail, including the coupling (between fluorine nuclei and other atoms), and chemical shift data that provides the assignment of both the location and nature of fluorine atoms within a molecule. But fluorine (^{19}F) exhibits some specific NMR properties that make it difficult to excite and decouple from other nuclei. Importantly, any new 'multinuclear NMR spectroscopy' approach, centred on ^{19}F NMR, lacked a robust routine HFX probe that could do every experiment well – until recently.

Opportunities ahead

Modern NMR probes often allow easy, straightforward use of ^{19}F NMR or ^{1}H and ^{13}C NMR, but not all three at the same time. JEOL's response was the introduction of the ROYAL HFX NMR Probe (see box overleaf) and a dedicated matrix of complementary 1D and 2D NMR experiments (Figure 1). The ROYAL HFX NMR Probe offers the ability to manipulate the ^{1}H, ^{19}F, and ^{13}C spins simultaneously without the typical loss in performance associated with traditional NMR probes designed for proton-fluorine NMR spectroscopy.