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An introduction to the special issue on *pharmaceuticals, drug discovery and natural products*

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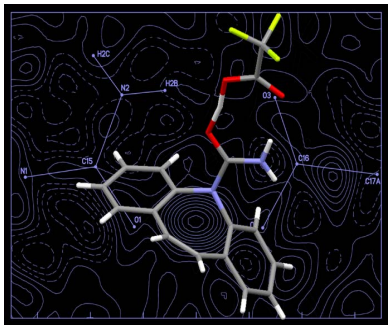
Back in January, I was invited by both Sandy Blake and Tony Linden to contribute to the relaunch of *Acta Crystallographica Section C* by acting as the Guest Editor of a special issue on **Pharmaceuticals, drug discovery and natural products**. As part of this relaunch, the style and format of the journal were to change to reflect the broader subject area of *Structural Chemistry* rather than the more limited area of *Crystal Structure Communications* and, in addition, the scope of the journal expanded to include all aspects of structural chemistry, even where a crystal structure is not reported, for example, computational and NMR-derived structures and structure prediction.

Whilst preparing this special issue, I was absorbed, as I suspect most crystallographers were, by the continuing celebrations of the Bragg centenary of modern crystallography which was marked by a special symposium and the 'Two Braggs exhibition' at the recent ECM28 meeting in Warwick. As we approach the beginning of the International Year of Crystallography, IYCr2014, I was drawn to re-read '*Selections and Reflections: The Legacy of Sir Lawrence Bragg*' (Thomas & Phillips, 1990) and '*The Development of X-ray Analysis*' (Bragg, 1975), and in particular those recollections of early researchers in the field of pharmaceutical molecules. The pioneering work of Dorothy Hodgkin and investigations of the complex structures of cholesteryl iodide (Carlisle & Crowfoot, 1945), penicillin (Crowfoot *et al.*, 1949) and vitamin B_{12} (Brink *et al.*, 1954) stand out as remarkable achievements for that time. The structure solution of cholesteryl iodide was one of the earliest examples of the use of a heavy atom to dominate in fixing the phase of the structure.

For work in the field of solid-state pharmaceuticals and the optimization and development of active pharmaceutical ingredients, small-molecule single-crystal and powder X-ray diffraction are both crucial analytical techniques that aid in the fundamental understanding of these systems. The questions that are being asked today of these substances have not changed significantly from the past, such as molecular structure, polymorphism issues, absolute configuration and absolute structure, and more recently the question of H-atom positions to establish whether a material exists as a salt or cocrystal phase. The question of polymorphism also presented itself in the work of Carlisle and Crowfoot during their investigation of the structure of cholesteryl iodide, and two crystal forms, A and B, were identified from the morphology and unit-cell determinations. These same original crystals were rediscovered some 50 years later in a drawer in the X-ray laboratory at Birkbeck College. They were in a tin which was labelled in Harry Carlisle's handwriting and the vial clearly contained crystals of two different morphologies. I had the rare privilege of working on these original crystals of cholesteryl iodide to fully elucidate the structures of each polymorphic form (Palmer *et al.*, 2006). The subject of polymorphism in pharmaceutical materials is an emotive one. First and foremost it is a regulatory requirement that you can demonstrate control of your process to ensure that you produce the same crystal form each time a batch of the material is synthesized. In addition, some polymorphs can demonstrate utility or benefit such as a desired solubility or stability, and in this case it is possible to gain some form of intellectual property to protect the use of these solid forms in the formulated drug product. A consequence of this intellectual property is that the question of polymorphism is often debated in court rooms the world over, and from my observation, in these cases it is often money that triumphs over science. That said, I have been present at trial hearings where a solid *Acta Crystallographica Section C* paper has successfully closed off such avenues of alchemy.

Possibly the most frequent request for structure analyses of pharmaceuticals materials and natural products is for the determination of absolute configuration. For the final drug substance, knowledge or proof of the chirality is again a necessary regulatory requirement.



The subjects of absolute configuration and absolute structure were covered in the *Acta Crystallographica Section C* virtual issue on **absolute structure** (http://journals.iucr.org/special_issues/2012/absolutestructure/) and as noted by Howard Flack in his editorial for that issue, 'the validation of absolute structure and absolute configuration determinations is a thorny subject.' Nonetheless, practitioners in this field have to make the best use of the tools available in order to make this regulatory commitment. For light-atom structures, the ability to collect highly redundant data sets with Cu $K\alpha$ radiation has assisted in these determinations. Also, the utilization of some *a priori* knowledge of the chirality from the synthetic pathway or salt formation using a known chiral auxiliary or counter-ion, for example, (*R*,*R*)-tartaric acid, can assist in the assignment of the absolute configuration. More recently, the application of statistical methodologies, such as the determination of absolute structure using Bayesian probability statistics on Bijvoet differences (Hooft *et al.*, 2008, 2009, 2010) and the application of 2AD plots (Flack *et al.*, 2011), have significantly aided in the validation of the assignments.

One final issue that is pertinent to the pharmaceutical community and has been a topic of discussion recently is that of 'Salt or Cocrystal'. The formation of a cocrystal of an active pharmaceutical ingredient can often utilize the acid–base interaction as a driver for cocrystal formation. In cases where the difference in the pK_a (ΔpK_a) of the active ingredient and coformer is small (typically less than 1), there can be ambiguity in the description of the final state. Knowledge of whether the material exists as a salt or a cocrystal at ambient temperature is extremely important, as the new FDA guidelines (*Guidance for Industry. Regulatory Classification of Co-Crystals*, 2013) suggest that the regulatory pathway for a salt is very different to that of a cocrystal material which is now considered as a 'drug product intermediate' rather than a new entity.

Finally, I would like to sincerely thank all of the authors who have contributed to this special issue of *Acta Crystallographica Section C*. The timeless questions of polymorphism, stereochemistry and H-atom position are present and discussed within these papers and the structural data presented originates not just from X-ray analyses, but also from NMR and computational studies, thus fulfilling the requirements of the new format of the journal. I am certainly looking forward to what the future holds for *Acta Crystallographica Section C: Structural Chemistry*.

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