Cocrystals can help to address the manufacturability (flow, compaction, processability) as well as solubility/dissolution, hygroscopicity and stability properties of an active pharmaceutical ingredient (API). In addition, the greater flexibility afforded by the various different cocrystal manufacturing approaches offers significant pharmaceutical, bio-pharmaceutical, intellectual property, as well as cost saving advantages over other more established API solid state forms. Cocrystals would also appear to have great utility for non-ionisable APIs, which do not form salts, but also for ionisable APIs where salt formation has proved to be difficult if not intractable.

However, these very clear opportunities are potentially constrained by an uncertain regulatory pathway. In 2013 the Food and Drug Administration (FDA) defined cocrystals as drug product intermediates (DPIs), deeming that the conformer is an excipient; in contrast, the European Medicines Agency (EMA) in 2014 defined cocrystals as being solid state variants of the APIs, aligning them with salts, polymorphs, hydrates or solvates.

The problem is that there appears to be no universally agreeable definition of cocrystals. There does appear to be a general consensus that cocrystals are homogeneous crystalline materials comprised of at least two different components with defined stoichiometry, however, the disagreement is centred on the properties of these constituent parts. The FDA went on to define cocrystals as “solids that are crystalline materials composed of two or more molecules in the same crystal lattice.” The FDA also indicates that, “traditionally, pharmaceutical solid-state forms of an API are grouped as either polymorphs or salts. Cocrystals, however, are distinguishable from these traditional pharmaceutical solid-state forms. Unlike polymorphs, which generally speak only within the API within the crystal lattice, cocrystals are composed of an API with a neutral guest compound conformer in the crystal lattice. Similarly, unlike salts, where the components in the crystal lattice are in an ionic state, a cocrystal’s components are in a neutral state and interact via non-ionic interactions.”

These definitions support the Agency’s current regulatory viewpoint, that is to say that co-crystals are dissociable “API—excipient” molecular complexes that should be treated as drug product intermediates (DPIs) and not as different variants of the API. As such the FDA guideline has encountered extensive criticism from the scientific community – both in academia and industry. In contrast, in the EMA’s reflection paper, their position is more aligned with the industrial and academic views that cocrystals are in fact different forms of the API.

There will undoubtedly be many cocrystals that will form polymorphs, hydrates or solvates. This is likely to cause significant regulatory confusion if these different forms need to be fully described in the drug product section of the regulatory application, rather than in the API section. Similarly, the exact description of cocrystals/salts can sometimes be open to significant uncertainty, and there can often be a salt-cocrystal continuum. For example, the crystal structure of escitalopram oxalate shows one oxalate dianion and one neutral oxalic acid molecule for every two escitalopram cations. Thus, di-escitalopram oxalate is cocrystallised with oxalic acid, and can be viewed as being a cocrystal as well as a salt. Indeed, there are some marketed APIs that were approved as salts, but are in fact cocrystals, for example, caffeine citrate or escitalopram oxalate. In reality, there are doubtless many other examples where pharmaceutical salts are in fact cocrystals. However, some commentators have questioned whether it really matters whether a molecular ‘complex’ is either a salt or cocrystal, as long as the underlying design intent is achievable.

Thus, a fundamental understanding of physical/chemical mechanisms underpinning any physical change(s) are essential during drug formulation development and should be part of any Quality by Design drug development strategy.

However, it would appear that scientific understanding is not a constraining consideration in the industrial uptake of cocrystals, but rather it is the regulatory uncertainty and specifically the different approaches favoured by the FDA and EMA, that is likely to slow their more general usage.

References