Forensic investigation on an amorphous solid dispersion batch: Mitigation of 1.5 years project delay

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Purpose
Compound A is developed as a spray-dried dispersion (SDD) to provide improved solubility and oral bioavailability. The lead SDD composition is 50:50 % (w/w) Compound A: HPMCAS-M and is used to manufacture a solid oral dosage form for clinical use. During a recent SDD manufacture, the GMP API batch was not fully dissolved in the spray solution which led to a physical mixture consisting of the SDD and crystalline material. Identification of the root cause and subsequent reprocessing strategies ensued.

Methods
A variety of methods were used for both characterization and troubleshooting. Powder X-ray diffraction (PXRD), crystallography, thermal analysis and 19F ss NMR spectroscopy were used as characterization techniques. Solubility determination were used to facilitate SDD reprocessing.

Results
After significant characterization was performed, a critical discovery was made. The batch was shown to contain an unexpected impurity: an isostructural hydrochloride salt of the target compound. Extensive solubility trials were performed that eventually resulted in the identification of a reasonable spray solution to reprocess the SDD batch.

Conclusion
The hydrochloride salt was shown to be the root cause for the crystallinity observed in the SDD batch. After obtaining more solubility information, the SDD manufacture process was redesigned and successfully reprocessed into a fully amorphous SDD.

Keywords: SDD, solubility, amorphous, isostructural, crystalline