Development of a robust API crystallization in a multi-component solvent mixture: Using high throughput automation as an enabling technology to develop comprehensive solubility maps

Authors: **Ben Cohen**[1], Michelle Mahoney[1], Brenda Remy[1], Jun Qiu[1], Chris Sfouggatakis[1], Zhongping Shi[1], Chenchi Wang[2]

[1] Chemical Development, Bristol-Myers Squibb Co.,
[2]Drug Product Science & Technology, Bristol-Myers Squibb Co.,

Session: 2B07 Crystallization of Pharmaceutical and Biological Molecules

Knowledge of solubility is essential to process design of API crystallizations. Detailed solubility enables a basis for defining robust and optimized process conditions, such as dissolution, seeding and isolation conditions. Determination of solubility maps is often performed by manual methods. However, as the number of components grows, and hence the number of possible process combinations grows, obtaining a comprehensive solubility map becomes more time-intensive. An example of this complexity was observed in the final crystallization of a BMS API currently in development. API solubility was found to be affected by numerous factors in the crystallization: the relative amounts of the three solvents, the amount of base, and the amount of reaction byproduct, as well as temperature.

To streamline the construction of the solubility map, a high-throughput workflow was developed to measure API solubility using automation equipment. The new workflow generated accurate solubility, with units of mass fraction through the use of an internal standard, over a wide temperature range. The data set enabled construction of a reliable solubility map which led to improved understanding of the crystallization. It helped establish process ranges around important operations such as dissolution, seeding, anti-solvent addition and isolation, as well as acceptance criteria for the upstream reaction and workup. The detailed solubility knowledge provided a basis for defining optimized process conditions within a robust design space.