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"panel of solubility experts" session at PCMDDD-4

Thermodynamic Solubility Measurement of Practically Insoluble Ionizable Drugs – Case Studies & Suggested Method Improvements

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Since mid-1990s there has been a heightened effort in drug discovery to predict aqueous solubility, described in at least a hundred publications (e.g., Huuskonen et al. 1998; Abraham and Le 1999; Jorgensen and Duffy 2000, 2002; Bergström et al. 2002; Hou et al. 2004; Delaney 2005; Dearden 2006; Taskinen and Norinder 2007; Wang and Hou 2011; Elder and Holm 2013; McDonagh et al. 2014). However, according to Faller and Ertl (2007), whose sentiment may be widely shared, "no really satisfactory approach to solubility prediction is available yet," in spite of the enormous number of prediction studies. Recently, the "Solubility Challenge" (Llinàs *et al.* 2008; Hopfinger et al. 2009) has spurred fresh discussion about prediction efficacy and quality of available data.

The most cited challenge to good prediction has been the difficulty to access enough high-quality, drug-relevant, and sufficiently-diverse solubility data that adequately cover the chemical space of drugs (and hopefully of research compounds).

Measuring high quality data is expensive and analytical-resource consuming. Even with great expense, quality is not ensured when results are determined from poorly-designed assays, potentially limiting prediction accuracy. Selection of prediction training set molecules which are ionizable without consideration of the effect of pH also mitigates accurate prediction. There are many other factors that contribute to data quality.

To address some of the above concerns about data quality, a panel of experts will discuss ways (i) to improve the quality of future measurement of thermodynamic solubility and (ii) to normalize existing data for pH and temperature effects to extract useful intrinsic solubility values.

The panel of experts will comprise of several invited speakers, each presenting a 20 minute talk in a Tuesday evening session. The moderator will make a brief introduction. The presentations will be followed by an audience discussion.

- The objective of the panel of experts will be to discuss the best practices for the saturation shake-flask measurement of solubility as a function of pH (still the "gold standard" methodology), along with other promising methods, and to reach a consensus at the end of the session about the best approaches for studying sparingly soluble drug substances.
- The panel will be invited to write a "white paper" on the topic, to be submitted to ADMET&DMPK before year end. The moderator will write the first draft shortly after the meeting and circulate amongst the co-authors.
- Also, individual participants will be encouraged to submit separate papers to share their experience (as an opinion/review) or data (as original research article) in the general area of solubility measurement, to complement the "white paper."
- To be discussed are some of the factors which can affect the accuracy of thermodynamic solubility measurement:
    - incomplete dissolution over the incubation period
    - Higuchi's facilitated dissolution method to shorten incubation period
    - acid/base effected dissolution/re-precipitation method to shorten incubation period
    - adsorption to the filter or assay vial surfaces
    - poor wettability
    - inappropriate phase separation (e.g., by first centrifuging a saturated solution, then filtering the supernatant)
    - "promiscuous inhibitor" particles passing through filter
    - formation of drug-buffer complexes, drug aggregates/oligomers (dimers, trimers, ...), micelles
    - polymorphs, hydrates, solvates, amorphous form
    - not using buffers with ionizable drugs
    - using unnecessarily high buffer concentrations (e.g., causing drug-buffer complexation)
    - not measuring the pH of the equilibrated saturated solution of ionizable drugs
    - effect of impurities, especially those which are ionizable
    - compound instability
    - not sufficiently sensitive analytical methods used to determine very low drug concentration