Pharmaceutical evaluation of early development candidates: Miniaturized and automated early Polymorphism investigations

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During the last decade polymorphism and other physical quality related aspects have emerged to key factors within pharmaceutical development strategies. The increased awareness of the effect that polymorphism may have on pharmaceutical key parameters like bioavailablility, manufacturability and stability of the drug product and patent related motivations triggered the implementation of sophisticated high-throughput polymorphism investigation processes both in-house and/or through outsourcing partnerships with specialized companies, and let to regulatory recommendations [1].

Since the number of new chemical hits intended for pre-clinical and clinical development increased tremendously over the recent years [2], there is a strong need to select the best compounds from a pharmaceutical "developability" point of view [3]. However, the "traditional approach" of relatively late investigation and selection of the most suitable polymorph within the development value chain may cause avoidable delays in pre-clinical studies. On the other hand, the limited amount of drug substance typically available in the early development state compromise data quality and impede an early pharmaceutical assessment. The Aventis approach on early pharmaceutical compound profiling with the aim of providing high quality assessment requiring not more than 100mg of drug substance have been published recently [4].

The "solid state & physical quality" related part of this assessment comprising thermal, X-ray powder diffraction and Raman analytics and a 4 step polymorphism investigation strategy for early develop-ment candidates will be presented. In particular, the evaluation criteria, process and miniaturized analytical technology that can be applied for this purpose are discussed. In addition, theoretical considerations and statistical evaluations will be shared. The final goal of this polymorphism investigation strategy is to ensure a fast pre-clinical development of the selected candidate with already solved potential solid state issues due to early investigation and selection of the most suitable polymorph.

References

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