Facts and Fictions about Polymorphism: Personal Recollections of our Good Friend, Joel Bernstein

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Are polymorphs predictable? This question has been periodically raised in the scientific literature, and also in "virtually every legal confrontation on crystal forms", where the *nonobviousness* of polymorphs is debated. If polymorphs were truly predictable, they would all but be eliminated as potentially patentable intellectual property. Certainly, the claim in 1996 that "near future developments in computer speed and force field technology will enable the polymorph prediction of any molecular crystal" was never realized. But what is the state of affairs today? In this presentation, polymorph prediction is analyzed from two perspectives: statistics of polymorph appearance and computational crystal structure prediction (CSP). Facts and fictions about polymorphism revealed through statistical analysis of crystallographic data from the Cambridge Structural Database and over 229 solid form screens conducted at Hoffmann-La Roche and Eli Lilly and Company are presented, along with combined experimental and computational CSP studies of model pharmaceutical compounds. The work, in collaboration with and inspired by Joel Bernstein, not only shows that polymorphism is unpredictable on the basis of molecular structure, but it also shows the substantial gap that still exists between crystal structure prediction and polymorph realization. In Joel's words, "each compound constitutes a new challenge and the prediction and realization of targeted polymorphism remains a holy grail of materials sciences".