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## Raman Spectroscopy in Crystallization

Real-time understanding of small molecule or biopharmaceutical solid form

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### Introduction

Safe and efficacious medicines have benefit to patients, clinicians, pharmaceutical companies and regulatory agencies. Two trends in the regulatory landscape have created new scientific opportunities and financial motivations for using process analytical technologies (PAT) in small molecule and biopharmaceutical manufacturing. The first trend is increased inspection and enforcement, post-approval inspections, records inspection, and compliance with requiring generic drug manufacturers to register with the FDA. In 2015, the FDA reported a 40% increase in preapproval inspections of generic drug manufacturers between 2011 and 2015.<sup>1</sup> The second trend is a shift toward using Quality by Design (QbD) principles in brand name and generic drug manufacturing. In 2002, the U.S. Food and Drug Administration (FDA) launched an initiative to encourage innovation in manufacturing technology and quality system approaches. The FDA 2004 PAT framework strongly emphasized a shift from tested-in quality after the drug product was produced to building in quality throughout production with "continuous real time quality assurance".<sup>2</sup> In 2003, the European Medicines Agency (EMA) established a PAT team, which released guidance documents released on process PAT, QbD and real-time release testing. International Conference on Harmonization (ICH) Q8, Q9, Q10 and Q11 documents reinforced FDA and EMA guidance, which has been implemented in the USA, European Union and Japan since 2009. Importantly, these documents provide guidance on developing an approach to understand and manage risks that might affect critical quality attributes.

### Solid State Form, Crystallization, and Polymorphism

One critical quality attribute of a pharmaceutical product, whether it is a small molecule or biopharmaceutical, is its solid-state form. The solid-state form can be crystalline or amorphous, depending on the molecule and how it is processed. Crystalline refers to a form having a regular structural order, polymorphism refers to the ability of a molecule to crystallize in more than one crystal form, and amorphous refers to a form which has no long-range structural order. Salts, co-crystals, hydrates, solvates are other possible solid forms. Crystallization is a process used to crystallize a product from its primary reaction. Other methods of forming a solid state product are freeze drying and hot melt extrusion. Regardless of the technique, the process must be carried out in a controlled manner to consistently yield the correct form. This whitepaper will focus on the crystallization process, but the assessment principles can be applied to other processes that produce a solid-state form.

Crystallization is important in small molecule drug substance, or active pharmaceutical ingredient (API), production because the API crystal form affects the drug product's bioavailability, compressibility, safety and efficacy. In biopharmaceutical products, the crystal form affects functionality, solubility, purity, stability and aggregation propensity. Most API

## Raman Spectroscopy in Crystallization

Two trends in the regulatory landscape have created new scientific opportunities and financial motivations for using process analytical technologies (PAT) in small molecule and biopharmaceutical manufacturing. One critical quality attribute of a pharmaceutical product, whether it is a small molecule or biopharmaceutical, is its solid-state form. Raman spectroscopy is a valuable PAT for crystallization applications such as molecular understanding of solid form, polymorphism, in situ real-time monitoring, and confirmation of the solid form. The molecular specificity, ability to be directly coupled to a reaction vessel, and compatibility with solids, liquids, gases, and turbid media are advantages of Raman spectroscopy. Readers will be introduced to recent successes in Raman-based monitoring and control of API and biopharmaceutical crystallizations.

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