

# WHITE PAPER ENSURING CONSISTENCY IN POLYMORPHIC DRUG SUBSTANCES AND PRODUCTS:

When and How to Apply a Specification Limit



# INTRODUCTION

## ENSURING CONSISTENCY

To ensure the quality of pharmaceutical products, manufacturers must characterise and quantify their physical nature throughout all phases of development—beginning with the drug substance, or Active Pharmaceutical Ingredients (API), and over the product's entire shelf life. Preferably, the substance registered with regulators will be of a single, solid-state structure where there is no possible variation in the drug product's stability, dissolution, and bioavailability. It is also acceptable to develop a mixture of two stable polymorphs, provided that the ratio of one to the other does not change during the product's shelf life.

However, at various stages of formulation, production, and storage, other physical forms can be induced to form unintentionally. When these different polymorphic forms do not share the same physical properties, their presence can affect the product's safety and efficacy. Manufacturers must, therefore, be aware of such possibilities and have methods for detecting and controlling the degree to which the drug substance or finished product converts to another form.

When it is possible for different polymorphs to be formed, a quantitative test, such as a limit test, should be applied to all production batches of the product to ensure that the degree of polymorphism falls within specified limits. Also, because the conversion to other polymorphic forms sometimes happens over time, limit tests must, in those situations, be applied over the shelf-life of the product. Many manufacturers have discovered this too late and have been forced to gather fresh stability data using a limit test, a step that can add months or even years to the development timeline.

The following paper is designed to help manufacturers understand when limit tests are needed and to plan for them proactively. It also provides an overview of the recommended methodology (X-Ray Powder Diffraction, or XRPD).

### POLYMORPHIC PURITY AND CONSISTENCY

Over half of all drug substances exhibit polymorphism; that is, in their solid state, they show diversity in how their molecules and ions are arranged inside the crystals. They, therefore, exist as more than one structural type. This is the case whether they are formulated in a single component system (pure base/acid, non-ionizable) or in a multi-component system (salt, hydrates, solvates, co-crystals, and racemates). Drug substances can also exist in an amorphous state in which the molecules or ions are randomly oriented. Amorphous material can consist of one or even more components e.g. amorphous salts, dispersions (See Figure 1.).

The potential for different polymorphic forms to exist within the same targeted drug substance is of significance because different forms of a crystal can have different physical and chemical properties, including solubility, hygroscopicity, density, chemical reactivity, melting point, transition point, and plasticity. Often these differences prove beneficial, and companies are encouraged to discover a compound's various forms early in the development process so that they might select the best candidate. Usually, innovator companies settle on an energetically stable polymorph for development, however, sometimes, the stable form is not found until later, for example when production is scaled-up, or when the whole process is fine-tuned post submission to regulators.

For all manufacturers, the goal for the final dosage form (tablet or capsule) is to have polymorphic purity and consistency—in other words, to have but one crystalline form in the pill or tablet for its entire shelf life. When this is not the case, and the compound is a mixture of different polymorphic forms, or when the form is not stable, the compound's stability, dissolution, and bioavailability can change. Any such change can directly affect the drug's safety and efficacy. For example, anhydrous and hydrate forms of a compound might have dramatically different intrinsic solubility profiles—a factor that will impact how the drug is absorbed into the body.

Since metastable polymorphs exist in a higher state of energy than stable polymorphs, they will, over time, convert to stable polymorphs—a process that is accelerated when the polymorph is highly soluble. This transformation can happen at any time—in a matter of minutes, weeks, or years, depending upon the specific system and environment. Manufacturers must, therefore, be attuned to such potential phase changes and monitor them over the shelf life of the product.

Manufacturers generally choose to develop the stable form of a drug substance because it will have the least potential to convert to another form<sup>1</sup>. However, companies—especially generics manufacturers—sometimes purposely target metastable (unstable) polymorphs when they show some advantages over stable polymorphs in terms of their macroscopic properties, such as power flow, bulk and tapped densities, reduced hygroscopicity, or enhanced chemical stability. Targeting a metastable polymorph can also enable a generics manufacturer to file an Abbreviated New Drug Application (ANDA) with the U.S. Food and Drug Administration (FDA) under Certificate IV, demonstrating that it is not infringing upon the innovator patent.

Batches of drug substances are usually pure forms. In some rare cases, however, they may be a mixture of two polymorphs. This is acceptable provided that the manufacturer knows the solubility for each crystalline form and has controls in place to ensure that all batches contain the same percentage of each form.

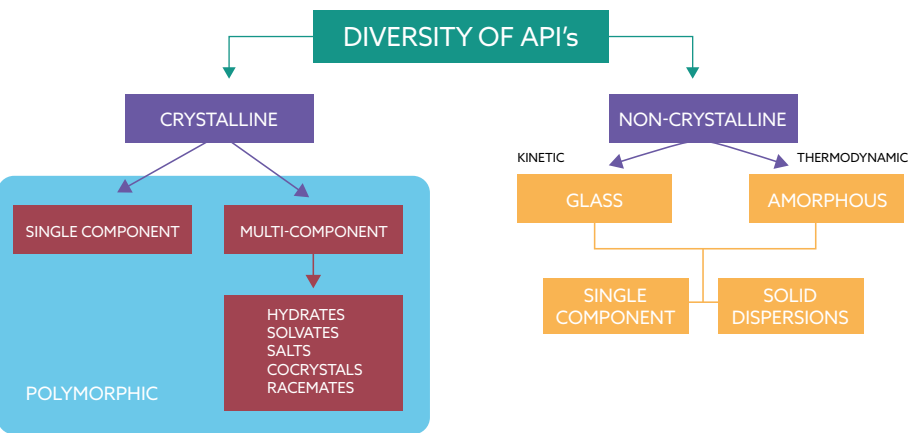


Figure 1: Diversity of Solid State Forms of Active Pharmaceutical Ingredients

MANUFACTURING AND TRANSFORMATION OF FORMS

Polymorphic transformation can occur at different stages of drug development, as seen in Figure 2, and can be affected by different manufacturing processes and by inappropriate storage.

Pure drug substance can change during industrial processes such as isolation, filtration, drying, micronisation, de-lumping, and sieving. Final dosage forms (meaning the drug substance and any excipients) can change during any robust production process, such as granulation, mixing with excipients, compression, blending, and spray drying. The introduction of excipients into a drug can make it either more or less stable.

Both pure drug substance and final dosage forms can be transformed through exposure to various environmental conditions (different temperatures and humidity levels) during storage.

In order to control product quality, manufacturers must, through experimentation, understand under which conditions one polymorph will change to another.

They then must find ways to optimise their production, applying process controls to avoid potential transformation, and follow release specifications so that each batch is consistent. When the appearance of a new phase is detected, manufacturers must be able to ensure that the amount of the new form resides within acceptable limits.

REGULATORY REQUIREMENTS

It is becoming increasingly important to quantify crystalline phases precisely and accurately in order to satisfy regulatory concerns about the safety and efficacy of drug substances and products. Manufacturers are required, as part of their applications for new investigational drugs and submissions for marketing approval in both the U.S. and E.U, to provide data to regulators on whether changes in a drug substance or drug product affect its performance.

Guidelines from the International Conference on Harmonization, ICH Q2 (R1)<sup>2</sup> specify that manufacturers must have validated and reproducible methods for characterising and controlling polymorphs throughout the approved expiration dating of a drug. This should begin with analysing the drug substance, maintain the chemistry synthesis and drug release stages, and continue monitoring the stability of ongoing batches.

ICH guidelines Q6A<sup>3</sup> specify the use of X-ray Powder Diffraction (XRPD) to characterise, monitor, and control crystalline forms as an acceptance criterion for new drug substances and drug products. (See “How X-ray Powder Diffraction Works,” below.)

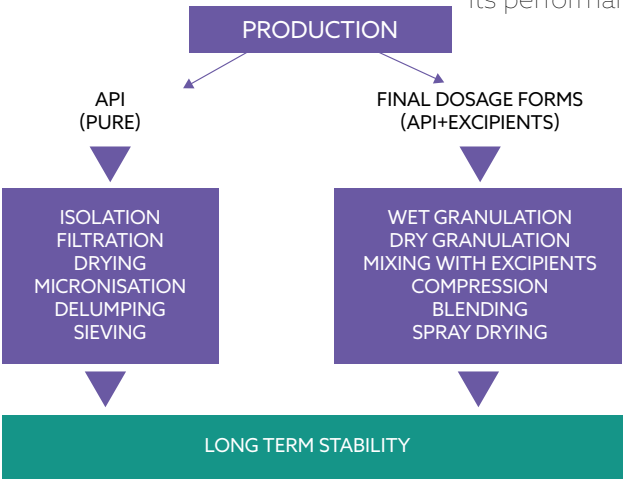


Figure 2: Points of Potential Polymorphic Conversion

ESTABLISHING AND MONITORING THE PRESENCE OF POLYMORPHS

The decision tree from ICH presented in Figure 3 illustrates the process that manufacturers should step through in characterising, measuring, and monitoring the polymorphic content of their drug substances/products. All drug substances should be screened to assess polymorphs. When multiple forms exist, they must be characterised. Furthermore, when the polymorphs are found to have different properties (such as solubility) that can affect the product’s safety or efficacy, the manufacturer must establish and conform to limits on their presence.

PRE-RELEASE BATCH TESTING

Even when manufacturers can control the presence of polymorphs with known solubility rates, they need to minimise batch-to-batch variation. This means that prior to release, each batch must be tested to ensure that it resides within the set limits. If the drug product performance testing provides adequate control of polymorphic ratio changes, the manufacturer simply needs to establish acceptance criteria for the relevant performance test.

TESTING OVER THE SHELF LIFE

When that is not the case—in other words, when the degree of polymorphism is not sufficiently controlled by the performance test—the manufacturer must continue to monitor for polymorphs over the course of a two-to-three year stability test.

It is possible that during the stability test, the manufacturer will observe changes in the product’s crystalline structure which will impact safety or efficacy. At that point, the manufacturer must establish acceptance criteria that are consistent with the desired safety and efficacy levels and proceed to apply them over the shelf life of the product.

Thus, manufacturers should foresee this scenario and plan for it. Should they fail to do so, they could experience a serious—even catastrophic- setback in the development and approval timelines. Developing and validating the limit test alone can take months, depending upon the availability of the material. The limit test then must be applied over the shelf life of the product which could be a matter of years. It is otherwise impossible to demonstrate that the product passes the limit test until it reaches its expiry date.

Almac has identified three conditions that are likely to lead to the need for a limit test to be conducted over the entire shelf life of the product. In any of these situations, companies are strongly urged to be proactive in creating the limit test PRIOR to beginning stability testing. In this way, they can avoid the lengthy delays imposed by the need to start over in developing a limit test and collecting stability data. These situations are:

- An anhydrous crystalline form of the drug substance is developed into the drug product, while the existence of a hydrated crystalline form of the substance is known. If the anhydrous form is not carefully packaged and stored, it may absorb water from the air and convert to a hydrated form.
- An amorphous form of the drug substance is developed into the drug product when crystalline forms are known to exist. Residual solvents or moisture (left over from spray drying or granulation, for instance) may initiate crystallisation of the material.

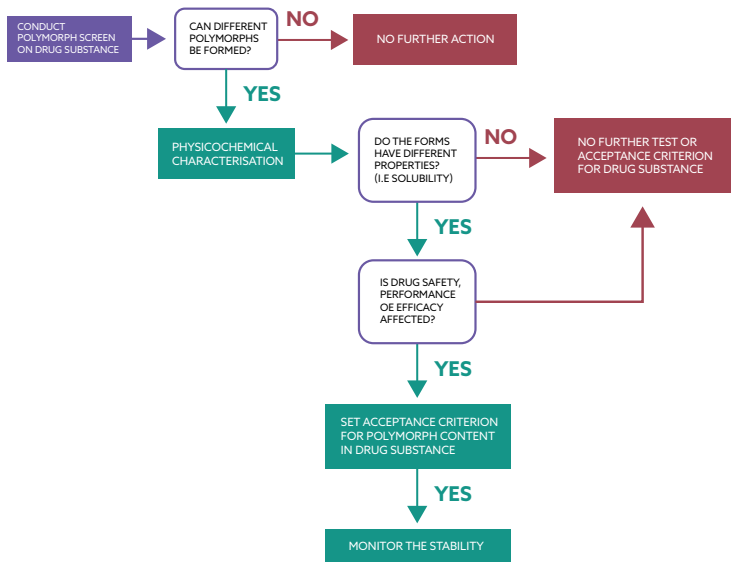


Figure 3: Decision Tree. Specification settings for drug substance and drug product (ICH Q6A)

- A metastable form of the drug substance is developed into the drug product. While this is more often the case with a generic form of a drug, it can also be characteristic of an innovator compound. Adding excipients as part of the formulation can alter the stability of the drug.

HOW X-RAY POWDER DIFFRACTION WORKS

X-Ray Powder Diffraction (XRPD) is regarded as one of the best techniques to use in identifying the phase of a solid and in performing a limit test. Whilst there are other techniques, XRPD has the advantage of being easy, inexpensive, and quick. The XRPD method, being rapid and non-destructive, is the method of choice by laboratories worldwide for identifying and quantifying characteristics of drug products.

Pharmaceutical crystals are usually made up of neutral, organic molecules and/or organic ions that are arranged in regular arrays. Crystalline organic compounds are characterised by a long-range order of building units (molecules) in three dimensions. This means there is high order present in the crystal, and molecules are repeated according to the elements of symmetry. Therefore, it is possible to recognise the minimum volume (unit cell) inside the crystal, and by repeating strongly defined symmetry rules, to build the whole crystal.

The parallel planes of atoms within a crystal are equally spaced from one another by a certain value: d spacing, which can be calculated by knowing the wavelength of

the incident beam. Therefore, the atoms in a crystal can diffract X-rays (bending them at an angle) to scatter them coherently.

In XRPD, crystalline samples are irradiated with a monochromatic beam of known wavelength. This wavelength diffracts inside the electron cloud of the crystal's individual imagined planes consisting of atoms at an exact angle (theta). The scattered rays undergo constructive and destructive interference to produce a diffraction pattern, which contains information about the atomic arrangement within the crystal—specifically how the atoms are linked together and how the building units (for example, molecules) are oriented to one another in the bulk crystal. (See Figure 4.)

There are two main components of the diffraction pattern. The first is the line position, which corresponds to a certain crystal plane and is therefore characteristic for a crystalline state. The second is the peak intensity, or maxima, of the light intensity. Each compound produces a unique diffraction maximum that can be considered its “fingerprint” to identify the crystal structure of the compound. The intensity of the diffraction maximum is the sum of numerous factors related to the whole crystal structure, which also includes the chemical contribution (atom type) and, therefore, presents a basis for quantitative phase analysis.

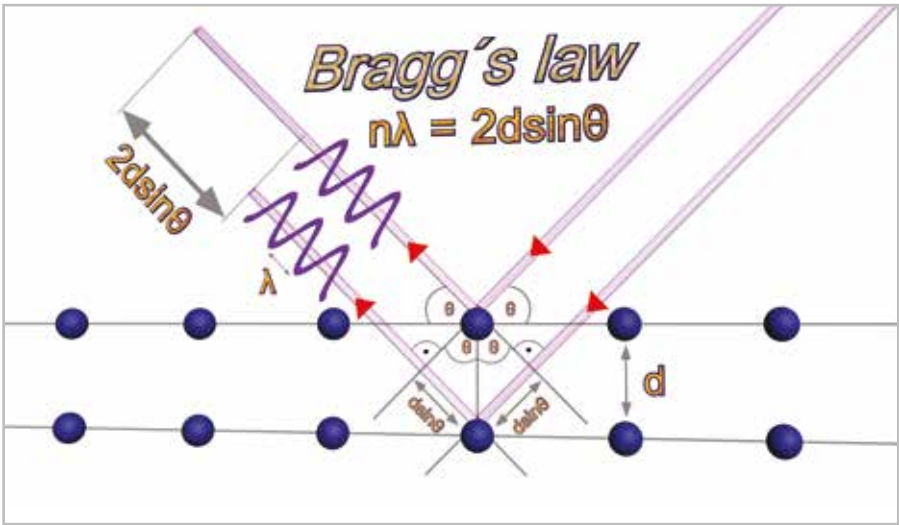


Figure 4: The creation of a Diffraction Pattern. Constructive interference occurs according to Bragg's law when n is an integer: λ- wavelength of incident rays, θ-angle between incident rays and the crystal surface, d-spacing between layers of atoms

TYPES OF TESTS

XRPD can be used to perform three types of tests in order to characterise a drug substance or for different purposes, as shown in Figure 5:

- Limit Test: a test to measure the percentage of a crystalline form that can be present without affecting product quality, in other words, the acceptable limit. Prior to performing a limit test, the manufacturer must know what quantity of the minor component is allowable and set specification level. This test needs to be performed when a certain amount of another crystalline form can potentially be present in a release batch, when another form can be created during storage, and when the drug substance is produced as a mixture of polymorphs.

- Detection Limit Test: a test for the minimum detectable trace of a crystal. For pure polymorphs, the limit of detection (LOD) using XRPD is often < 0.5 percent. When the drug substance is present in a diluted state in a matrix of inactive ingredients, the LOD is always higher. This test is recommended when traces of other polymorphic forms are known to initiate full batch transformation or when crystalline traces can significantly influence product performance such as dissolution rate. Detection limit test serves during patent litigation when it is necessary to prove that generic production batches do not contain traces of the innovator polymorph.
- Full Quantification: a method to determine the percent of crystallinity or other forms present. This test is required when a manufacturer is setting release specifications, when the drug substance is known to be produced as a mixture of polymorphs, and during stability monitoring. In quantitative methods, the calibration curves covering a wide range (0-100%, w/w) or a range of interest must show good linearity over the entire concentration range and exhibit a regression line equation with a high correlation coefficient.

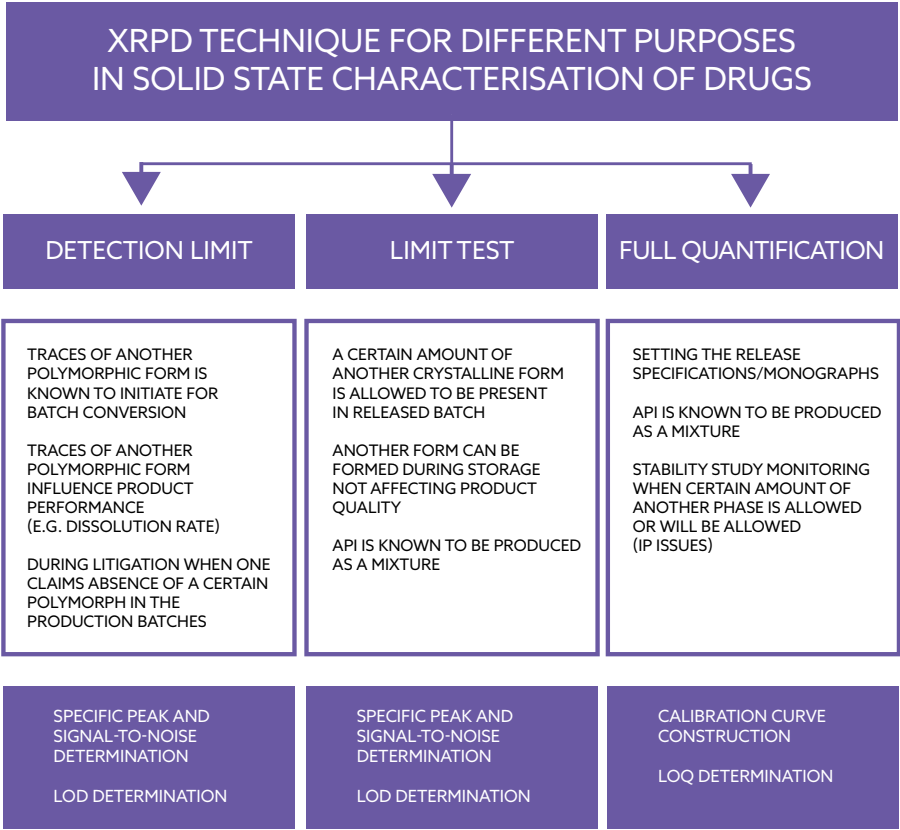


Figure 5: Use of XRPD in Solid-State Characterisations of Drugs

### LIMIT TEST DEVELOPMENT

The biggest challenge in developing a limit test on the final dosage form, as well as in the polymorph mixture, is in selecting unique diffraction peaks that cannot be confused with the peaks of another polymorph or of excipients, but possess the intensity needed for detection and quantification. The testing method must be validated to prove its accuracy and reliability in ensuring product quality and minimising batch-to-batch variations.

### ROBUSTNESS AND INSTRUMENTATION

Any errors in the intensity measurements expressed as peak height or the peak area of the diffraction lines will critically affect the accuracy of the results. There are numerous factors affecting XRPD analysis, and they can be grouped into three categories: inherent properties of the analyte, parameters relating to sample preparation, and instrumental factors. All should be considered or potentially tested during the development of the method to ensure its robustness, and the most critical parameters should be included in the method's validation protocols. The object is to prove that a small variation will not affect the results.

### INHERENT ANALYTE PROPERTIES

The major source of error in X-ray diffraction analysis is reportedly preferred orientation since it creates systematic variation in diffraction peak intensities.<sup>4</sup>

Due to the particle's morphology (plates, rods), we would expect crystals to always lie on the surface with the same orientation, their facets oriented in some order. This causes certain diffracted reflections from the sample surface to be enhanced, or for other reflections to be reduced. Since the quantitative method involves measuring the intensity of the diffracted beam (diffraction from certain crystallographic planes), this is the root cause of method error.

To minimise the effect of preferred orientation on the XRPD method results, different batches of testing material need to be explored. Sample uniformity should be ensured through sieving or by grinding the sample to reduce the particle size when mechanical forces will not affect the phase transformation.

### SAMPLE PREPARATION

Validation is performed on representative and homogenous samples. Representative samples must be as close to the production batches as possible in terms of particle size, morphology, and package properties. In contrast to other methods, achieving maximum sample homogeneity of a binary mixture is the biggest challenge for developing a successful XRPD method, and special care must be given to mixture preparation.

Optimisation of sample preparation (grinding, pressure), sample quantity, and selection of the best type of sample holder should be examined. For binary or multi-component mixtures, accurately weighed standards of the desired concentration are essential and should be prepared at least in duplicate.

### INSTRUMENTATION FACTORS

To get the best peak profiles and intensities, the parameters of the instrument need to be examined and optimised.<sup>5</sup> The configurations that can affect the incident beam include Soller, divergence and anti-scatter slits and mask, as well as the diffracted beam.

Different instrument set ups (such as transmission or reflection geometry) can be explored.

Lowering the scanning rate (step size) and analysis time will improve the sensitivity of the test so that more potential peaks can be detected. However, it will add to the length of the testing time.

The XRPD analysis is conducted in the standard calibrated Bragg-Brentano  $\theta$ - $2\theta$  geometry. The XRPD whole patterns are shown in the range  $2\theta$  of  $3^\circ$  and  $40^\circ$  and detection limit test are based on shorter scanning area. Samples are recorded using CuK $\alpha$  radiation at suitable tube tension at room temperature.

### SPECIFICITY AND LIMIT OF DETECTION ESTIMATION (LOD)

During method development peak specificity must be explored, and the peaks selected should be clearly separate from either any other polymorph or any excipient present in the formulation. For the limit test, it is important to distinguish between the real signal and noise. Signal-to-noise (S/N) ratios are usually calculated for the peaks in the average scans using the equation detailed in the European Pharmacopoeia (section 2.246). When a limit test is performed at a certain given level, limit of detection (LOD) can be estimated and during method validation, the process must be validated.

### LIMIT TEST VALIDATION

For the limit test, ICH guidelines require validation of specificity and limit of detection as a minimum. In addition, robustness can be tested and this usually relates to testing sample mass, tube intensity or day-to-day results comparison.

### GLOSSARY OF TERMS

- **Polymorphism** = existing as more than one arrangement of the building units in a solid state. Polymorphs share the same chemical make-up, but their molecules are packed differently.
- **Metastable** = a potentially unstable state because the substance spends an extended amount of time in a configuration other than the state of least energy
- **Amorphous** = a form that consists of molecules that are not ordered into a distinguishable crystal lattice
- **Anhydrous** = with all water removed
- **Hygroscopicity** = attracting or absorbing moisture from the air
- **Excipient** = a natural or synthetic ingredient formed alongside the drug substance



## CONCLUSION

Limit tests need not be performed in all circumstances; they need only be performed when a certain amount of another crystalline form can potentially be present in a release batch, when the drug substance is produced as a mixture of polymorphs, or when another form can be created during storage. However, it behoves manufacturers to understand when the test will be needed so that they can be proactive in developing, validating, and applying it. The consequences of not planning for a limit test—particularly when it is needed over the drug's shelf life—can be devastating.

The recommended methodology for performing limit tests is XRPD, as it has the advantage of being relatively fast, easy, and inexpensive.

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Dr. Edislav Leksic is the Team Leader of Physical Sciences at Almac Sciences. Edislav has worked in the pharmaceutical industry for the past ten years, with expertise in solid state chemistry related to API target selection, crystal surface property, scale-up and production troubleshooting. He was involved in preformulation work and development of complex systems such as solid dispersions and cocrystals.

Edislav received a Ph.D. in supramolecular chemistry from the University of Zagreb, with expertise in design and screening of pharmaceutical cocrystals and crystallography. Edislav has a strong GMP background and extensive experience from a generic industry perspective in managing the project in aspects of solid state chemistry and regulative perspective. Over the past several years he has worked closely with patent law authorities inventing new patent applications and contributing to aspects of IP.

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