

Abstract

To ensure the quality of pharmaceutical products, manufacturers must characterise and quantify their physical nature throughout all phases of development: from the Drug Substance (DS) to the final Drug Product (DP) and over the product's entire shelf life (Figure 1). Preferably, the substance registered with regulators will be of a single stable polymorph such that there is no possible variation in the DP's stability, dissolution, and bioavailability. However, at various stages of DS isolation, DP 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, quality and efficacy. Manufacturers must, therefore, be aware of such possibilities and have methods for detecting and controlling the degree to which the DS, on its own or in a finished DP, converts to another form. Here are presented limit tests used to detect low percentage of polymorphic entities within fixed-dose combination (FDC) tablets containing two DS (Figure 2).

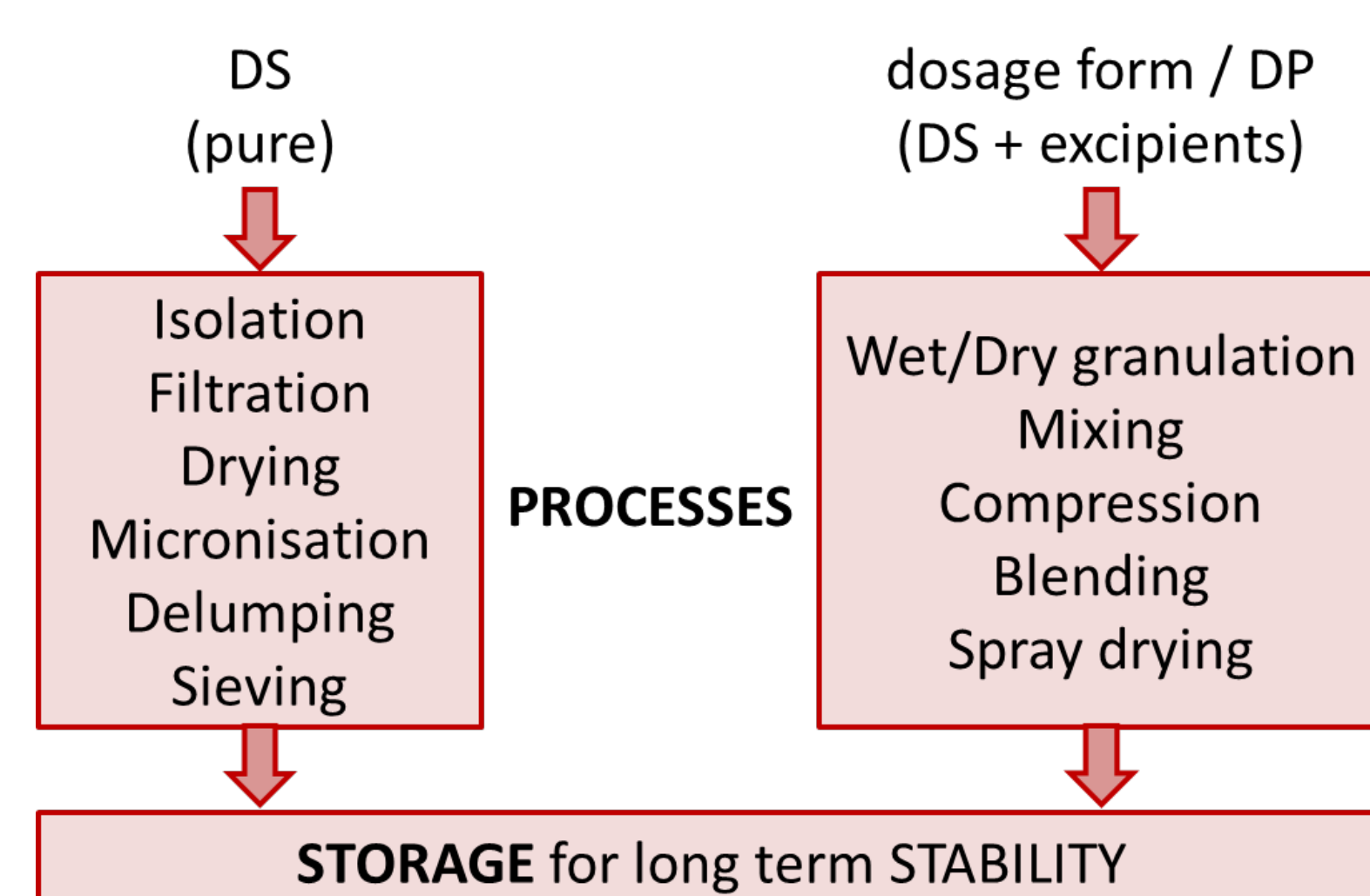


Figure 1. Different stages in production of a drug substance (DS) and of a drug product (DP)

Background

When it is possible for different polymorphs to be formed, a quantitative test should be applied to ensure that the degree of polymorphism falls within specified limits [1]. Since the conversion to other polymorphic forms can happen over time, limit tests must be applied over the product shelf-life. Guidelines from the International Council for Harmonisation (ICH) specify that manufacturers must have validated and reproducible methods for characterising and controlling polymorphs throughout the approved expiry date of a drug, Figure 3 [2,3].

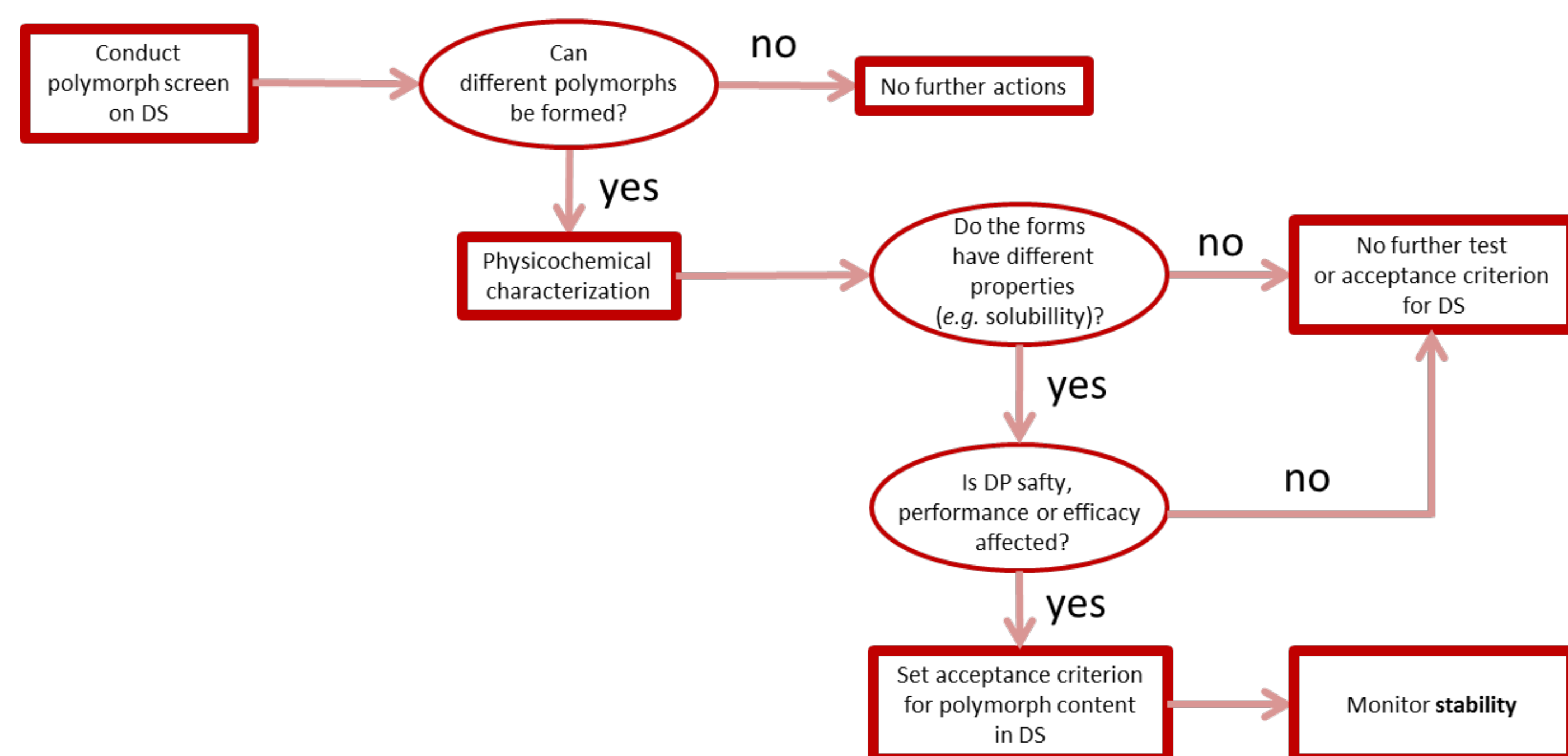


Figure 3. Decision tree from ICH Q6A [3]

Materials and Methods

Analyses were performed using a Panalytical X'Pert Pro diffractometer equipped with a Cu X-ray tube and a Pixel detector system. Samples were loaded into a 16 mm reflection sample holder to form a compact pellet. Alumina standards and samples were analysed using the instrument settings for Method SS and A-B, respectively (Table 1).

Attributes assessed during method validation were:

- System Suitability - method SS
- Specificity - method A
- Crystalline Reference Mixture homogeneity and detection limits - method B

Signal to noise (S/N) was measured manually, according to the *European Pharmacopoeia* (2H/h).

Peak net areas (cps) were also measured for the appropriate peaks in each preparation using the X'Pert Data Viewer software.

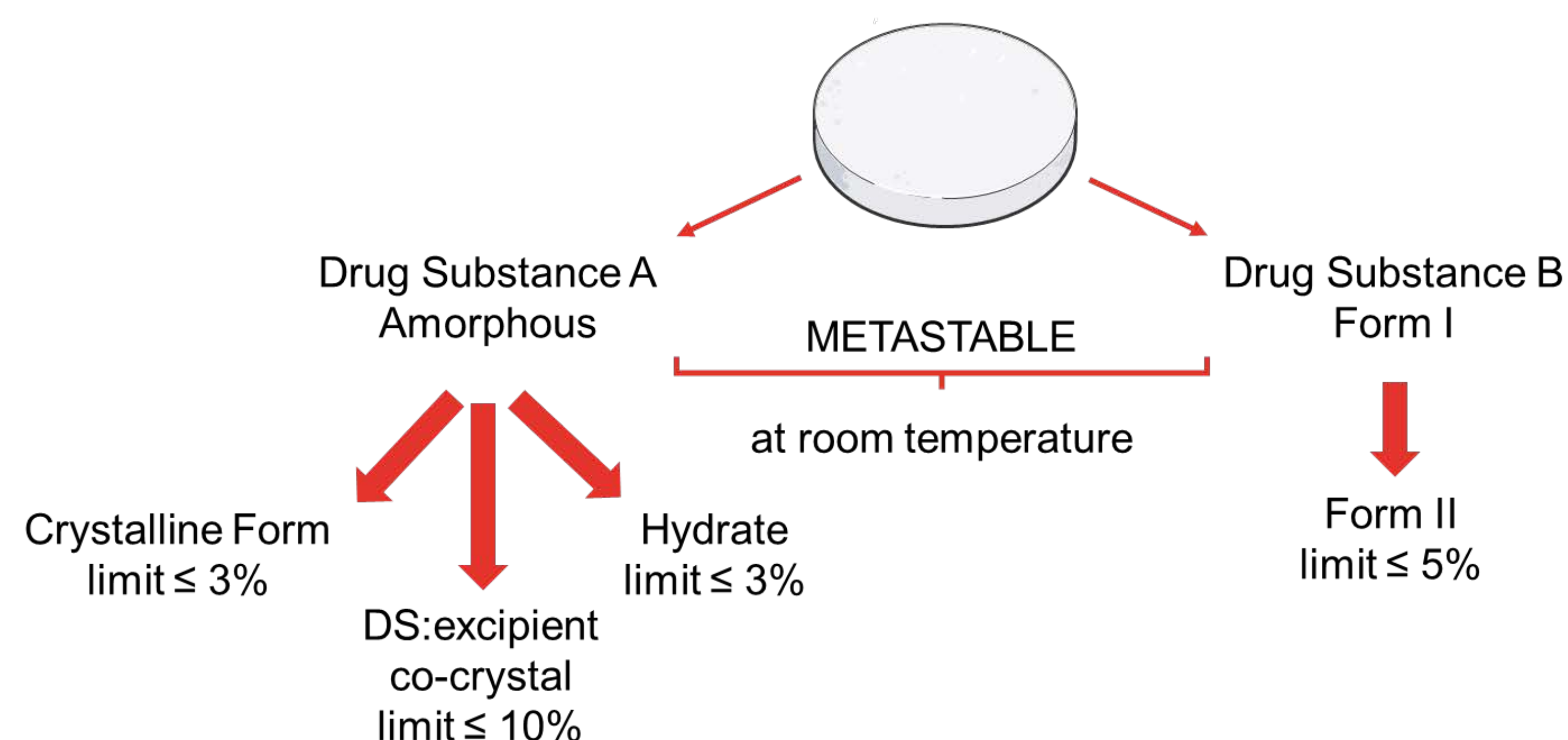


Figure 2. Summary of the limit tests validated for fixed-dose combination (FDC) tablets containing two DS

Table 1. Panalytical X'Pert Pro diffractometer instrument settings

Method	SS	A	B
Scan type	System suitability	Survey scan	Slow scan
Scan axis	Gonio		
Scan properties	Continuous		
Scan range (°)	34.0–36.2	3.0–40.0	3.0–13.0
Step size (°)	0.013		
Time per step (s)	186	161	1117 to 2392
Scan speed (°/s)	0.018	0.021	0.0014 to 0.0030
Number of steps	168	2818	762
Run time (min)	~5	~32	~74 to ~159
Spinner revolution time	1 rps	4 rps	
Beam path	Incident		Diffracted
PreFIX module	Fixed Div. Slit & Anti-scatter Slit		Pixel
Offset	0.000		
Soller slit	0.04 rad		
Divergence slit	Slit fixed 1° (SS) or 1/8°		N/A
Anti-scatter slit	Slit fixed 2° (SS) or 1/4°		Slit 9.1 (SS) or 7.5 mm Pixel
Mask	10 mm		N/A
Filter	None		Nickel (large)

Results

Almac successfully validated a detection limit method for four polymorphic entities in a fixed-dose combination (FDC) tablet containing two drug substances. Each form has a specific limit which has been validated via XRPD using reference standards.

Conclusions

XRPD is a recommended methodology for performing limit tests as it has the advantage of being relatively fast, easy, and inexpensive. It can be used to detect limits in three main scenarios (Figure 4).

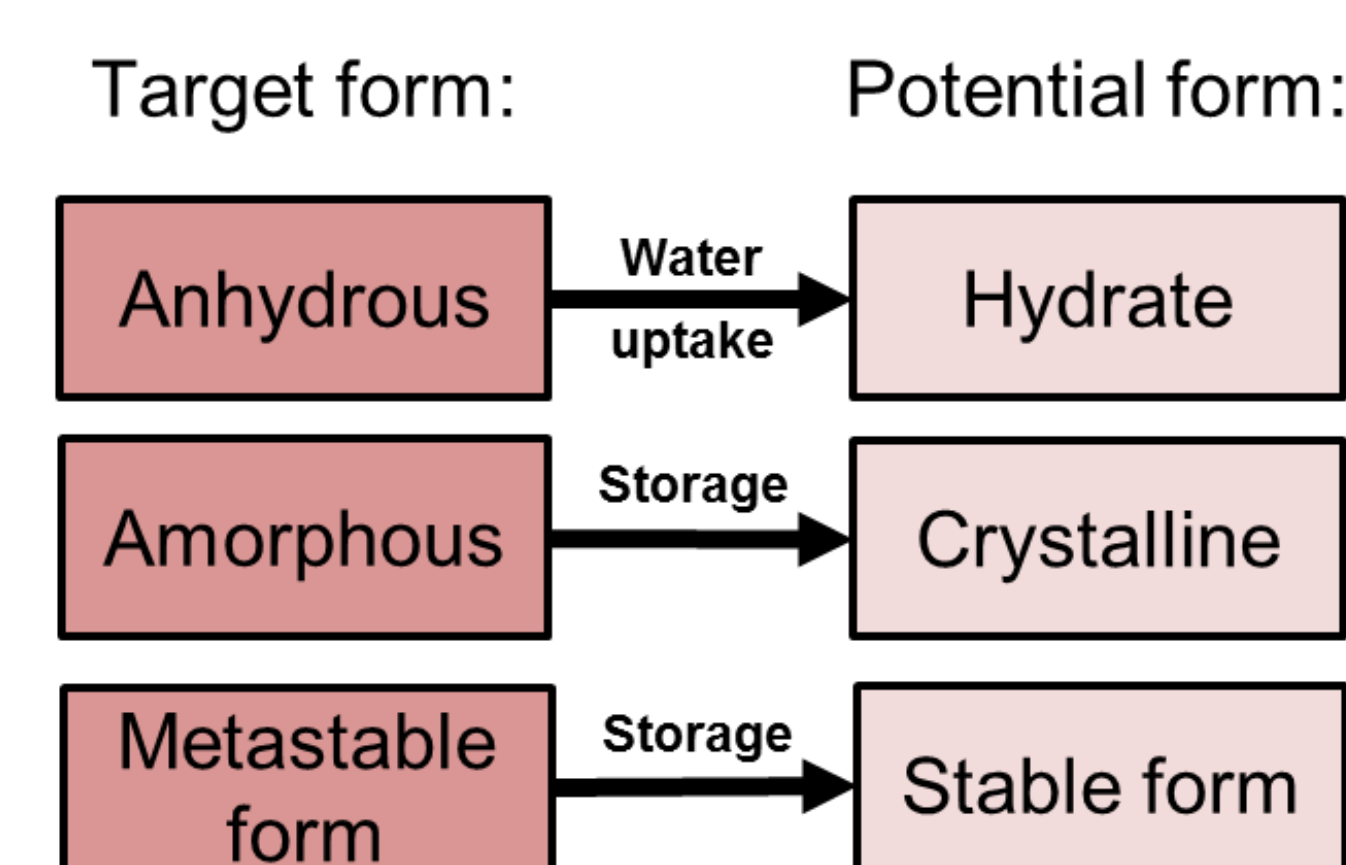


Figure 4. Three scenarios where limit tests can be employed to ensure DS and DP quality, efficacy and safety

[1] FDA, ANDAs: Pharmaceutical Solid Polymorphism, *Guidance for Industry*, July 2007

[2] ICH Q2 (R1), Validation of Analytical Procedures: Text and Methodology, *ICH Harmonised Tripartite Guideline*, June 1995

[3] ICH Q6A, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, *ICH Harmonised Tripartite Guideline*, October 2009