Amorphous Quantitation Strategy for Crystalline Drug Substance – a GSK Perspective

Peter Varlashkin
GSK, Durham, NC, USA
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Purpose

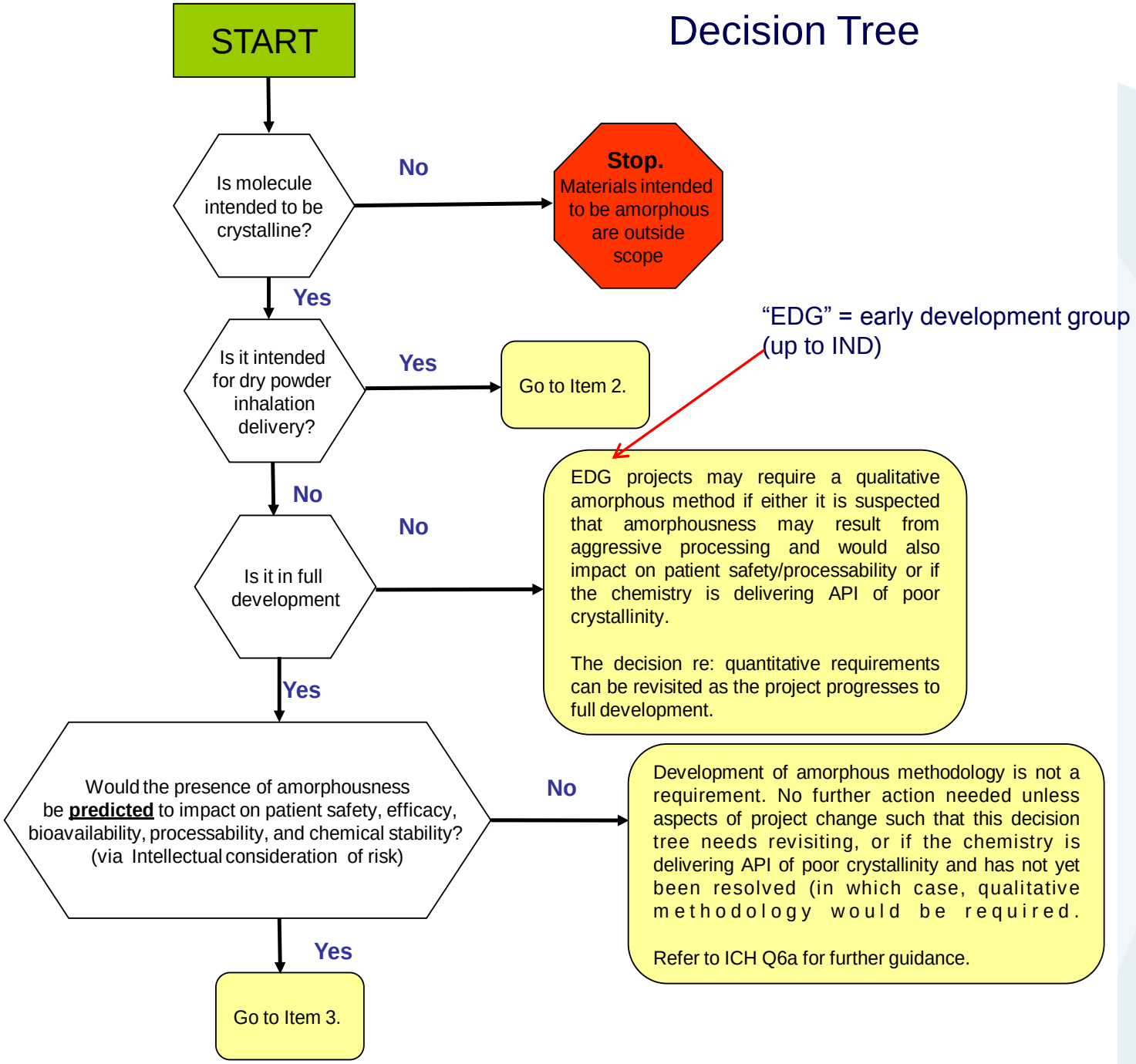
- To provide GSK perspective on when and how the residual amorphous component of crystalline drug substance should be monitored and controlled.

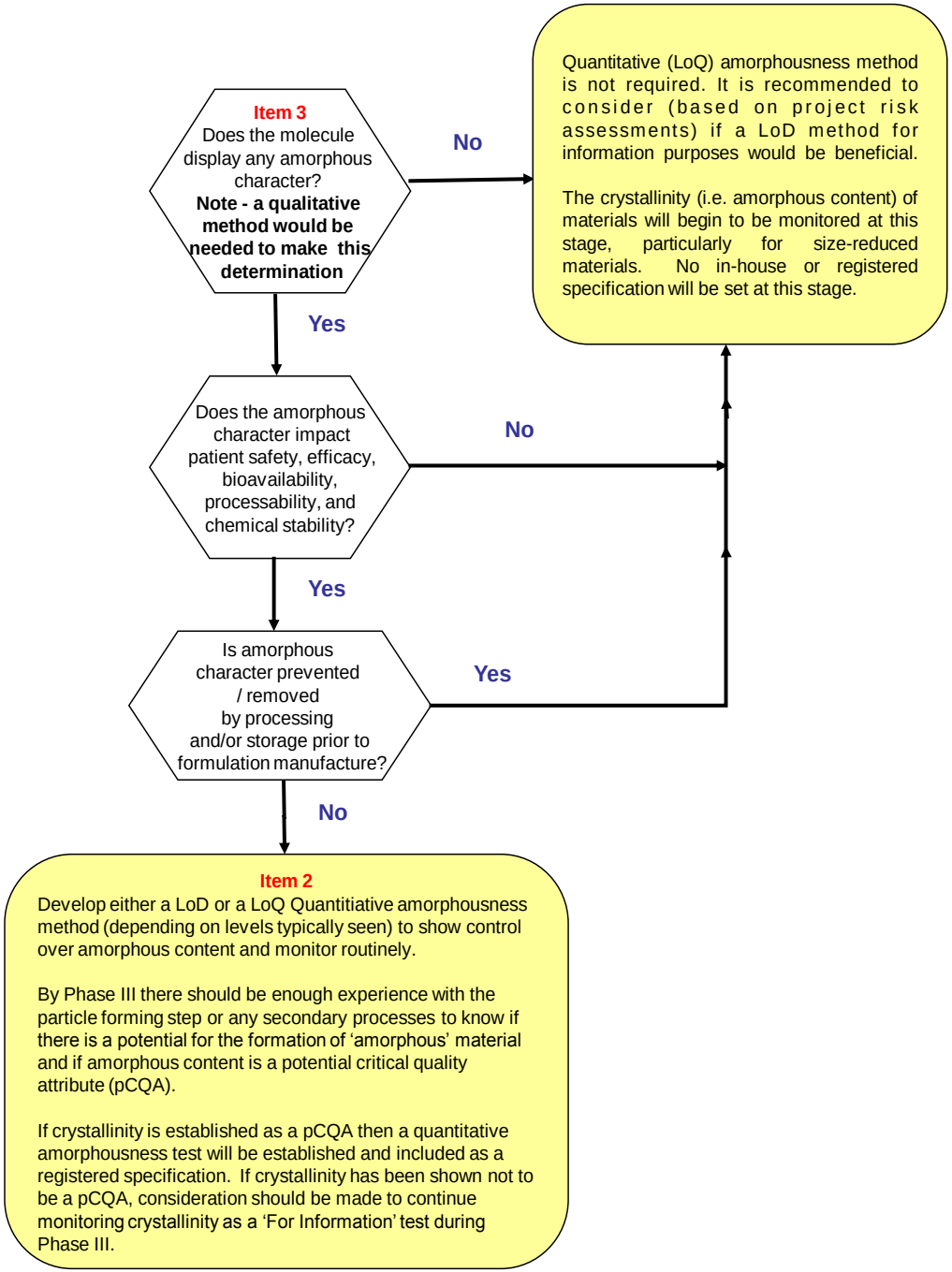
- For drug substance that is amorphous or converted to the amorphous state in the drug product formulation, the technical issues are different – detecting residual crystalline material in amorphous system. This is not the primary purpose for this presentation.

Internal (GSK) guidance document provides

- Short primer – what is amorphous and do you really have amorphous materials in your sample
- Amorphous Strategy – Decision Tree
- Choice of Technique
- Links to Technique-Specific Details
- Quantitation Strategy and Role of Standards
- Method Validation
- Consideration of Risk

Decision Tree




Item 3
Does the molecule display any amorphous character?
Note - a qualitative method would be needed to make this determination
No
Quantitative (LoQ) amorphousness method is not required. It is recommended to consider (based on project risk assessments) if a LoD method for information purposes would be beneficial.
The crystallinity (i.e. amorphous content) of materials will begin to be monitored at this stage, particularly for size-reduced materials. No in-house or registered specification will be set at this stage.
Yes
Does the amorphous character impact patient safety, efficacy, bioavailability, processability, and chemical stability?
No
Yes
Is amorphous character prevented / removed by processing and/or storage prior to formulation manufacture?
Yes
No
Item 2
Develop either a LoD or a LoQ Quantitiative amorphousness method (depending on levels typically seen) to show control over amorphous content and monitor routinely.
By Phase III there should be enough experience with the particle forming step or any secondary processes to know if there is a potential for the formation of 'amorphous' material and if amorphous content is a potential critical quality attribute (pCQA).
If crystallinity is established as a pCQA then a quantitative amorphousness test will be established and included as a registered specification. If crystallinity has been shown not to be a pCQA, consideration should be made to continue monitoring crystallinity as a 'For Information' test during Phase III.

Choice of Technique

- DSC – considered ‘first intent’ method – where possible
- GVS (DVS) – gravimetric vapor sorption
- XRD/IR/Raman – generally lacks adequate limit of quantitation/detection for residual amorphous content
- Other techniques such as SSNMR are not considered to be suitable for a quality control technique but may be considered when other choices are not an option.
- The reduction in specific surface area (SSA) may be used to track the reduction in amorphous over time, but other factors may also influence the observed changes in SSA value over time (such as loss of fine particle mass). Thus, SSA is not considered a primary technique for quantitating amorphous content in crystalline materials.

DSC

Advantages

Common instrumentation available on most sites
Relatively easily transferred
Good instrument to instrument comparability (including manufacturer to manufacturer)
No need for a recryst solvent (cf GVS)
More sensitive than XRPD
Quicker methods (especially with hyper DSC)
More easily quantitative than XRPD
Small sample quantity
Direct observation of the crystallisation event
Relatively simple method development
Less experimental factors to consider for robustness

Disadvantages

Generally less sensitive than GVS
Requires a clear sharp recryst to occur, or a Tg. Less sensitive if only a Tg present
Slow if modulated methods required
Small sample size (may not be representative due to poor amorphous content uniformity)
Analyst to analyst variability – manual integration, sample prep, and crimping of pan

Points to consider

- Thermal analysis should be used by first intent for the detection and quantitation of low levels of amorphous in crystalline material.

- GVS is best used for crystalline materials with low levels of amorphous and represents the best option if the amorphous content limit of detection/quantitation by thermal analysis is insufficient..

- It is possible to determine low levels of amorphous in crystalline material but the detection limit is compound specific. The amorphous content of some compounds may be so little or there is no interaction with probe solvents making the GVS approach not sufficiently sensitive or viable at all.

- GVS is typically the most sensitive compared to other techniques but is likely to be least robust. GVS methods rely on fast kinetics of re-crystallisation. Kinetics can be sensitive to a variety of parameters and hence, could be problematic from robustness point of view.

- For high levels of amorphous, linearity may be compromised so XRPD may be best option.

When to use

- To screen early development samples to identify those substantially crystalline and thus worth progressing to candidate selection.

- For samples containing greater than 10% amorphous noting that the ability to accurately fit an amorphous halo to the data depends on the complexity of the crystalline diffractogram.

- For the characterization of pure amorphous material used in the preparation of DSC and GVS standards.

- When small amorphous domains are present that would be missed by DSC and when material is not readily plastised by exposure to solvent vapour as required for GVS analysis.

Points to consider

- XRPD is best used for crystalline materials.
- Relatively high limit of quantitation for amorphous in crystalline samples

  ~10% w/w limit of detection/quantitation
- Peak broadening due to small crystallite size or strain may be confused for amorphous content
- Amorphous content can be estimated by XRPD without the use of standards by deconvolution of the powder pattern
- Calibration curves can be generated with standards but may be unnecessary (see prior bullet point)
- Compared to Raman, SSNMR, LOD/LOQ by XRPD is similar
- For low level (below 10% w/w), if possible, amorphous is best measured by thermal analysis or gravimetric vapor sorption methods

Quantitation Strategy and Role of Standards

- Recommend tracking and trending amorphous based on an analytical response in preference to a % w/w value.
- For DSC, this might be the heat of crystallization of amorphous in J/g.
- Percent w/w values by different techniques (DSC vs GVS) may be different due to kinetic differences or due to measuring amorphous in the bulk (e.g. DSC) versus possibly measuring amorphous at the surface (GVS).
- Amorphous standard generated by ball milling or freeze drying may not represent surface amorphous from high energy processes such as milling or roller compaction.
- Amorphous standards should be primarily used to establish the nature of the amorphous response and assist with method development rather than enable % w/w amorphous levels to be reported.

- Percent w/w amorphous values may be generated as part of method development or validation to provide a means to link the relative instrumental response to an absolute % w/w value.

- If regulatory authorities ask for an absolute % w/w value during product license review, an “approximate” % w/w number can be provided for information.

  However, any replies to the regulatory authorities should clearly identify that any absolute % w/w amorphous determinations are limited to the level of characterization of standards and how closely the standards mimic the amorphous material in samples.

- A relative response provides a satisfactory means to report and ultimately limit (if necessary) the amount of amorphous content in QA-released drug substance or drug product.

Method Validation

- Principles of method validation for other techniques such as HPLC may be applied to physical properties quantitation methods such as measuring amorphous content buy with certain caveats.
- Not all aspects of validation applied to HPLC may make sense for physical properties methods.
- Accuracy is harder to assess for physical properties methods. The best approach, when possible is to compare with another method such as SSNMR.
- SSNMR is a “nuclei-counting” technique that does not require external standards to produce a % w/w result.
- Quality by Design (QbD) principles such as the use of method risk assessments, etc can be applied to physical properties methods.

Consideration of Risk

- The impact of residual amorphous on the end user – patient, can be assessed with a variety of risk assessment tools such as Failure Modes Effects Analysis (FMEA).
- The approaches used to assess the impact of amorphous material on the drug product performance may be similar to assessing the impact of any ingredient of the drug product.
- Various parties involved in pharmaceutical and chemical development, primary and secondary manufacturing, drug metabolism and pharmacokinetics, safety assessment, and CMC regulatory should participate in the risk assessment.

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