

ICH Guidelines on particle properties

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Analysis of particle properties of a drug substance is required in order to understand and control the drug product. When developing a new drug product you want to make sure that it is stable during storage for a certain period (usually some years). Thus, it is very relevant to know what happens when it is exposed to, for instance, higher temperatures or humidity (degradation?). Further, the drug substance should be *bioavailable* when given to a patient, i.e. it is necessary to know the behaviour with regard to solubility and dissolution.

Thus, as the particle properties are of essential importance in relation to patient safety, these are mentioned in several places in the ICH guideline. This short paper, will give you an overview of ICH guidelines related to *particle control*. In the other guidelines you will find information about requirements in relations to stability of you product (ICH Q1A-Q1F) and for Analytical Validations (ICH Q2), when you have identified the methods you need in order to control the product.

If you want to know more, or if you need help in any issue related to particle characterization, do not hesitate to contact info@particle.dk. Having customers all over the world – including many of the leading pharmaceutical companies, we have been involved in all kind of issues related to pharmaceutical powders - and will for sure be able to help you.



ICH Q8(R2) on Pharmaceutical Development

In the guideline regarding Pharmaceutical Development, following is stated regarding particle properties:

- *“The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g. solid state properties) should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity and permeability. These properties could be inter-related and might need to be considered in combination”*

Thus, what this guideline says is that you have to know the properties of your particles – otherwise you will have no control when the drug product is given to the patient. The relevance of some of the mentioned parameters are quite obvious: Of course the solubility should be known: If the drug product does not dissolve when given to the patient, it will have no effect. Further, the water content should be known: A drug substance with a high content of water might be very prone to degradation, as water most often induces side reactions (e.g. with excipients in the drug product).

This is also why it is stated, that the parameters might need to be considered in combination: Could a higher water content or particle size affect, for instance, the solubility? The relevance of particle size and crystal properties will be discussed in next section.

In the same guideline it is stated, that the requirements for being in control does not only apply to the drug substance, but also to the excipients: *“The excipients chosen, their concentration and the characteristics that can influence the drug product performance.....”* should also be in control – including their interactions with the drug substance.



ICH Q6A on Specifications

According to ICHQ6A, following is stated in relation to particle properties:

- *Particle size: For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing the particle size distribution should be carried out using an appropriate procedure and acceptance criteria should be provided.*

So, what does this mean? Does it mean that you only have to have control of particle sizes if they have a significant effect on the mentioned parameters? Yes, this is actually what is stated – but when can you claim that this is the case? And what does significant mean?

For highly soluble particles, the risk that these will not dissolve is of course limited – but still: What if the particle size is >1 mm – would it still not be a problem? Furthermore, how would you examine the tendency of different particle sizes to interact with excipients in the final drug product? Can you be sure – without testing - that particle size does not affect stability? Even though the wording in the guideline might be a little vague, the intention is clear: In all cases you have to make a risk assessment. And if you cannot rule out that particle size has an effect, you need to carry out analyses and to set specifications.

On polymorphic forms of the particles (i.e. crystal properties), following is stated:

- *“Polymorphic forms: Some new drug substances exist in different crystalline forms which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug product. In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.”*



Again: Even though the guideline uses words as “in some cases”, it could more correctly be translated into: You have to know exactly what form (crystal/amorphous/hydrate) is used, as all forms have different properties and will therefore affect performance, bioavailability or stability. Because all polymorphic forms do have different properties – this is in the nature of the crystal, as the individual drug molecules are attached differently to each other: A different binding pattern will inevitably lead to difference in, for instance, solubility. However, in some cases, the differences between these forms might be very limited and/or the solubility and stability of the drug substance very high (refer to www.particle.dk for more information about polymorphs). In these cases the need for control is somewhat lower than in cases where the drug substance has a limited stability. Also, you should know whether the crystal form (polymorphic form) in development is actually the more stable form: If a metastable form is used, a risk of transformation will exist, which will lead to a lowering of solubility and change in stability. If such a change occur all stability experiments etc have to be repeated. Thus, conclusion: Secure that you are in control!

ICH Q9 on Quality Risk Management

The last guideline that should be mentioned in relation to particle properties is ICH Q9, which does actually not state anything specific about particles: However, this guideline sums up the importance of evaluating the risks!

- *“The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and*
- *The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.”*



When you have made a thorough risk assessment, it will be straight forward to define which parameters you should have under control: From the risk evaluation on the specific drug substance/drug product you will be able to evaluate, whether particle size should be kept under strict control, as small variations will affect bioavailability – or if the limits could be set very broad, as it isn't critical to the performance. Thus, this latter guideline is very closely related to ICH Q6A: Specification can only be set when you know the criticality of the individual parameters.

At Particle Analytical we can perform all tests related to particles properties – and furthermore, we are able to help you set the optimal specification limits for controlling the drug product. Do not hesitate to contact us at info@particle.dk for questions or a quote.

