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Warning Letters

A greater frequency of warning letters issued by the FDA in the first nine months of 2017 are increasingly monitoring the manufacturing process. Strict adherence should be applied to the ICH Q6A guidelines, particularly to ensure patient safety

Søren Lund Kristensen
and Dr Harm Otten at
Particle Analytical

Over the years, communication in the form of published warning letters mentioning requirements for particle characterisation from the FDA has increased. They raise awareness of the control of particle properties of active pharmaceutical ingredients (API) and excipients in manufacturing and the final product (1). Among the wide range of properties that shall be tested, the ICH guidelines topics Q6A and Q8 exemplify particle size, water content, solubility and crystal properties (2). However, they do not seem to be in place everywhere at ingredient suppliers and medicine manufacturers, as underlined by the FDA warning letters. By law, the possibility to carry out validated and approved analysis methods need to be ready before the start of routine production, but may already prove essential in early developing phases. These are needed to set meaningful specifications and later control the out-of-specification (OOS) in-processes.

Thorough screening and the use of correlated methods ensure the suitable specifications for the solid form, be it organic or biological. Highlighted in this article are the effects of particle properties on manufacturability (flow, size control, general handling), pharmaceutical window distortion (by shift in size distribution and dissolution) and patient safety. This information is very helpful for maintaining control over the manufacturing process.

In the past five years, FDA warning letters referring to particle characterisation numbered between one and three, but, in the

first three quarters of 2017, four had already been sent out. On the basis of ICH guidelines, these intercept the possibility of the manufacturer or resell to import or sell specific products in the regulatory region issuing the letter: the US, which is the most important pharma market today.

The requirements include a solid understanding of the physical properties of particles, reflected in set and controlled specifications for API and excipients. The lack of particle characterisation inclusive of size control and failure to set specifications is a common theme in the warning letters. To know and control these at various steps of the drug manufacturing process puts the company producing the product in a safe spot with regard to regulatory compliance, audits, technical production properties, efficacy of the drug, batch-to-batch variation and the safety of the patient.

Minimal Guidelines

The organisation of the most important medical regulators on the planet is called ICH (2). Their current membership includes the following five regulators: Health Canada; European Commission; Ministry of Health Labor and Welfare/Pharmaceuticals and Medical Devices Agency (Japan); Swissmedic; and FDA. There are also three industry organisational members: European Federation of Pharmaceutical Industries and Association; Pharmaceutical Research and Manufacturers of America; and Japan Pharmaceutical Manufacturers Association.

Of the 60 guidelines to date on quality, safety, efficacy and multidisciplinary topics, one is particularly important in the context of this article: the ICH Quality Topic Q6A on ‘Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances’ (2). This forms the basis for appropriate analytical characterisation of drug substances and excipients.

ICH Q6A and Decision Tree

The Q6A guideline urges each of the manufacturers and suppliers to reassure themselves if the suitable specifications for the chemically synthesised API and excipients are set. Biotechnological, biological, radiopharma, oligonucleotide, herbal and fermented drugs, as well as crude drugs of animal or plant origin, are covered elsewhere.

The specifications typically originate from the development phase and interact closely with efficacy of the drug, such as therapeutic window/dose-effect-relationship, bioavailability, toxicological profile, stability and so forth. They also form part of the overall current Good Manufacturing Practice (cGMP) framework with suitable facilities, validated processes and analytical procedures, root-cause investigations of OOS, raw-material and in-process testing.

A suggested approach for deciding whether and which specifications are needed is given in the ICH guideline in the form of a decision tree (see Figure 1). Liquid dosage forms are left out of the focus of this article, but shall adhere to corresponding

standards, especially if a tendency to precipitate or clog, existence of emulsion or suspension is the case or if the like is observed. Particle size becomes a significant factor and may play a role in five aspects: solubility (dissolution and bioavailability); processability; stability; content uniformity; and appearance.

This list is not complete, but highlights the areas of influence for particle size and the need to set specifications. If none of these is expected – which is very unlikely – it would also require experimental proof of no effect. At a minimum, the characterisation of a new drug product in this setting must contain: description of size, shape and colour, discriminative identification of API, assay for strength and content of API and impurity characterisation (4).

For particle size determination, quantitative acceptance criteria and specifications on the basis of development research must be set. Analysis should be performed at release (4). Acceptance criteria are ideally known from the development phase or may be part of a validated series of experiments later. Additionally, the particle size distributions might not be constant over time that is, “the potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account” (4).

Example Warning Letters

A common theme is the appropriate characterisation of particles, as can be seen in a blackened FDA warning letter 320-17-33 from 2017:

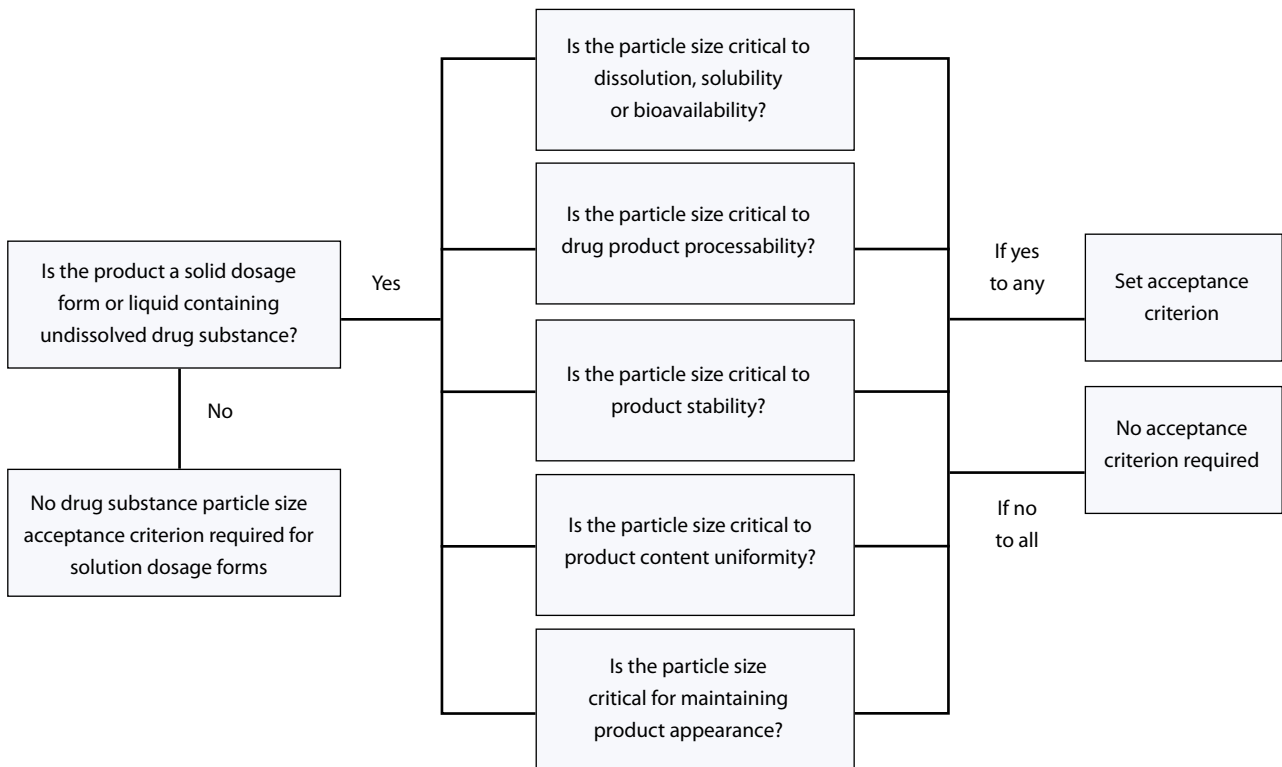


Figure 1: Scheme of the ICH Q6A decision tree

“Validation sampling plan for XXX API... In your response, you acknowledged that a higher level of sampling during the revalidation of the manufacturing process revealed some inter-batch variability in residual solvents and particle size distribution of XXX... Your response is inadequate because it did not describe how your continued process verification program assures that quality attributes continue to be met batch-to-batch, as well as uniformly throughout each batch. Regarding uniformity, using only XXX samples for attributes that may significantly vary within a batch is insufficient” (3).

Here, on top of the sampling procedure, one can also see how the in-process analysis of particle size plays a role in dialogue with the authorities, with regard to this urgent prevention of importing the drug product. Here is another example from 2017:

“We reviewed your response, received June 1, 2017, which included blank, revised production records, and find it partially adequate... However, the form also includes a single blank line for each of the following: particle size, head space, glass check and sealed. The critical factors specified in the scheduled process need to be measured and recorded at intervals of sufficient frequency to ensure the factors are within the limits specified in the scheduled process” (3).

This points directly to the requirement of regular validated particle size measurement. This should be done by correlated methods – such as laser diffraction and microscopic photo analysis – but is of course dependent on the size distribution range of the particles in question.

A third and final example letter is from 2008: “We note that at the time of inspection your firm had failed to study, among other things, the washing process and particle size, as well as how they impact product quality and function” (1).

This again shows the importance of in-process control, but points towards the more significant implications on product quality and function when no analysis or specifications are chosen. The efficacy of the drug and its homogenous distribution in the final product are related to particle size.

Patient Safety

These controls are needed to set sensible specifications and later monitor the OOS in-processes. A thorough screening and the use of correlated methods ensure the suitable specifications for the solid form, be it organic or inorganic. Leaving aside the particle properties effects on processability – flow, size control, mixing properties or general handling – particle size can have a major impact on the pharma window (5). A distortion of the plasma curve towards the toxic region may occur when the surface area is considerable larger, as is the case when smaller particles are manufactured.

Additionally, the solubility, dissolution and bioavailability characteristics heavily depend on the size distribution of the particle. Smaller particles tend to dissolve better, but validated results must be presented in all cases. In the end, one should overcome the lack of specification setting and regular validated control and use correlated methods to gather an overview of how particle properties can endanger patient safety.

Mitigating Risk

For specifications, the lower and upper end should be tested to ensure a safe space of operation and efficacy. In particular, Q6A advises to set acceptance criteria to tight: “Therefore it is considered inappropriate to establish acceptance criteria which tightly encompass the batch data at the time of filing” (4).

This decision could be too narrow and might not reflect in-process changes or manufacturing variability across sites. “Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance *in vivo*, as well as the intended use of the product” (4).

Here the correlation with dissolution rate data is made, which is relevant as it is one of the options to correlate particle size distributions from different methods, along with dissolution, solubility and bioavailability properties. Furthermore, the document suggests, “When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate” (4).

Everything that is produced is documented, validated and reproducible to the extent that it holds authoritative inspection criteria in audits every time and may be used in informed replies to regulators, as to the FDA. One should persuade authorities of proper in-house standards throughout the development and manufacturing processes. This should be started early in development and use validated correlated methods, which have proven comparable. One should note the expense of outsourcing method development, routine analysis early on and during development and manufacturing, as well as check on suppliers. They can justify the mitigated risk of wrong API identity, crystal polymorph, quantity or purity in product (6).

Last but not least, the safety of the patient and guaranteed performance of API in solubility and bioavailability must be continuously monitored. This will also help to re-adjust the set acceptance criteria to better fit real-life manufacturing variance and new information about bioavailability, among other benefits.

Anticipated Developments

Evaluating the trend towards more frequent warning letters and the not uncommon focus on particle size characterisation, no end is in sight. More common inspections of acceptance criteria are anticipated with a focus on particle size, coming from authorities worldwide, not only the 'Big Three' – EU (Switzerland, Norway), Japan and North America – but also, among others, China, India and South Africa.

Proactive behaviour to start the analysis and evaluation of criteria should be part of any pharma and generics development today. Automatically and securely sharing data of the most frequent analysis between manufacturing, QC and potential external partners will become a reality.

References

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About the authors



Søren Lund Kristensen is the founder and Chief Executive Officer at Particle Analytical, a Danish FDA- and DKMA-approved analysis company operating under cGMP standards for primarily pharma customers worldwide. He is an advisory board member for the Technical University of Denmark. Søren received his education from Royal Veterinary and Agricultural University (now Copenhagen University), Denmark.
Email: slk@particle.dk



Dr Harm Otten is a chemist working at Particle Analytical on a project basis. He received his education from Philipps University, Marburg, Germany and Copenhagen University, Denmark.
Email: harm.otten@gmail.com