Background

Quality by design (QbD) is a systematic approach to drug development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Definition and guidance related to QbD can be found in ICH Q8/Q8(R), Q9 and Q10. Pharmaceutical industry has extensive knowledge about critical product attributes for their particular medicinal product under development. For the benefit of patient safety and delivery of high quality products without extensive regulatory oversight, pharmaceutical industry is now more and more applying QbD in their development work.

The key factor of QbD is that quality is built into the medicinal product and a **Design Space** is proposed by the pharmaceutical industry and is subject to regulatory assessment and approval. For a particular medicinal product the design space may be dependent on the critical attributes of the active ingredient, the manufacturing process, the actual formulation, excipients and the packaging material. Thus, a strong understanding of the starting materials and processes used in the production of each medicinal product is vital.

As excipients are used in medicinal products and may affect both the characteristics of the product and the production processes, QbD in drug development may also impact excipient manufacturers. Accordingly, the suppliers may have a role to play in assisting the drug company to achieve their QbD objectives and a co-operation between the users and suppliers of excipients should be initiated and carried out in such a way to achieve a 'win-win' outcome for both parties. The pharmaceutical manufacturer will normally be the initiator of this collaboration and it is important to start a dialogue as early as possible in the development work, normally at clinical Phase IIB/Phase III.

This Questions and Answers (Q&A) document has been elaborated by a small working group consisting of representatives both from the suppliers and the users. It has been put in place to advise and give guidance on general questions that may need to be addressed at an early stage and to try and harmonise possible answers/comments from both sides in order to facilitate and rationalise in the starting up of collaboration in this field. The Q&A should be viewed as a living document and will be updated as more experience is gained by both parties.

Examples of Questions and Answers/Comments from excipient suppliers and users to be addressed in relation to QbD during development of medicinal products:

I. Effective communication between suppliers and users

Questions from the suppliers

1. How to initiate a dialogue and address the right people within a company?

Answer/Comment: *If the intention is to initiate a business dialogue, the supplier must contact the Global procurement staff, local procurement at the site or R&D procurement: when appropriate, procurement will communicate with personnel from other areas to encourage direct communication (e.g. scientific/technical expert for QbD). If you are a current supplier, then the Supplier Agreement and/or the Quality Agreement should have the company's contact details. It is important to stress that in the context of QbD development or change evaluation, a direct scientific/technical expert contact point would be needed.*

2. How to keep a good dialogue while still retaining proprietary information?

Answer/Comment: *Work with procurement to establish a Confidential Disclosure Agreement (CDA) separate from the Supply/Quality agreement. The scientific/technical expert contact points of the user and supplier should work together and be able to operate freely once the CDA has been put in place. Each group should document proprietary information exchanges, limit the number of personnel involved and work diligently to maintain integrity and trust.*

3. What kind of information should be shared: Critical Quality Attributes (CQAs) / Functionality Related Characteristics (FRCs), specifications etc?

Answer/Comment: *At the start of formulation development, the supplier should share a package of public knowledge information: excipient FRC, relevant specifications/characteristics, typical use examples/samples, GMP status, manufacturing source details, packaging and storage conditions, cost of goods, and confirmation that they are willing to enter into a long term supply agreement with a drug manufacturer.*

During exploration of the design space, a second package of information is needed to develop and execute a QbD protocol. The package should include basic process understanding as applicable, such as capability/control statistics for each FRC, control limits, consistency of raw material supply, in-process and release test results, excipient purity and evidence of stability in the commercial package. The Supplier may also be asked at this time to provide Regulatory audit reports and samples of excipient representative of the range of each FRC relevant to the formulation being developed. Please also see answers/comments on questions 24 and 25.

4. How can the resources that the supplier put into the documentation to support QbD questions from the user can be refunded, and how can this information be protected from other suppliers of the same material?

Answer/Comment: *The additional supplier documentation to define excipient processes in support of user QbD development should be looked upon as a future potential for the business of the supplier and a natural step in the initial communication between user and suppliers. The supplier could prepare a standard information package reflecting on the proven acceptable process parameters and the impact on excipient FRC with shared benefit to all users.*

Questions from the users:

5. How to establish good communication for administrative and technical questions while still retaining proprietary information?

Answer/Comment: *Dialogue between the excipient user and supplier needs to be established at an appropriate technical level at an early stage of excipient selection for a new project. This should be between the user company's formulators and the supplier company's application specialist. Proprietary information of both parties should be protected using a simple non disclosure agreement.*

6. How can information on Functionality Related Characteristics (FRCs) of the excipient be shared?

Answer/Comment: *The actual characteristics of an excipient which affect functionality in a drug product will vary according to the formulation and the manufacturing process. Dialogue needs to take place to cover which excipient characteristics may potentially vary from lot and lot and the user needs to assess whether these parameters will influence performance in their specific application. It should be noted that an excipient FRC may be critical in one drug product, but totally irrelevant in another.*

7. How to communicate changes that affect identified FRCs that you make to the manufacturing process and/or test methods on an ongoing basis?

Answer/Comment: *Supplier and user should agree in principle a suitable change control notification process which allows the user to make process enhancements, but also allows the user to verify no effect of the change.*

II. Development of the Dosage Form

Questions from the suppliers

8. Please provide information such as development phase, prior knowledge, special requirements (fast disintegration, controlled release etc), type of process (e.g. wet granulation, direct compression) and any specific requirements of the API.

Answer/Comment: *This is product specific information regarding the chosen pharmaceutical platform and is normally proprietary user information. However, under a CDA, some information may be provided to the supplier and thus allow the supplier to understand the excipient performance requirements and potentially demonstrate the excipient's generic utility to other users.*

9. What is the function of the excipient in the formulation: which functionality/functionalities do you wish to add to the dosage form and its process under development and which type of excipients, beside our product(s), are used in the product(s)/process?

Answer/Comment: *See above. Each product could have different requirements.*

10. Is the user willing to use robust production methods which minimise the effects of material variation?

Answer/Comment: *Achieving robustness is one of the goals of the formulation & process development included in QbD for the drug product. Depending on the criticality of the excipient, variations may or may not be acceptable.*
Our expectation is that the excipient we buy comes already from a robust production method, with consequently the quality variability reduced to a minimum. The robustness of the drug product process usually depends on the variation of the excipients. By choice of the formulation composition, manufacturing technique, and the settings of the process parameters we aim at minimizing the sensitivity of the product/process design for the normal material variation. If this doesn't work, we will have to ask for more narrow specifications on the materials (see also question 19).

11. Is the user willing to base their design space on excipient batch samples which reflect the normal production range of the material?

Answer/Comment: *Yes, in principle that is what we are looking for: samples representative of the full operating range of the process normally used to make the excipient. Therefore, the broadest normal/relevant range of specifications reflecting the excipient FRC should be sampled in support of drug product QbD.*

12. Is the user able to work with non pharma grades (eg food grade) in experimental work to define performance related characteristics?

Answer/Comment: *Where a Pharma grade is not yet available and it is very early in the development work, food grade material is acceptable for the non-GMP definition phase. However, we need to understand the difference between the two grades and why/how it should be relevant to use non-pharmaceutical grades.*

III. Questions related to excipient CQAs

Questions from the suppliers

13. Have you already determined the functionality related parameters (CQAs)/FRCs of our excipient related to your application?

Answer/Comment: *FRC's are to some extent known via literature and supplier information, or can be picked up during pharmaceutical development. During the QbD pharmaceutical industry investigates whether the CQAs/FRCs are indeed CQAs for the pharmaceutical product under consideration. The results should be shared to the suppliers under confidentiality. This would then support collaboration with the supplier.*

Questions from the users

14. Related to the particular dosage form, process etc, what FRCs are relevant to consider for this excipient?

Answer/Comment: *It is realistic to expect the user to have established experimentally which excipient parameters are important in a specific drug product application.*

15. What is the excipient batch uniformity and batch-to-batch consistency for the FRCs?

Answer/Comment: *The supplier can then confirm that the parameters identified in Q14 can be controlled with the excipient manufacturing process or not expected to vary from lot to lot.*

16. How are the excipient specifications (internal and external) for normal excipient production set and kept updated?

Answer/Comment: *In the majority of cases the specifications will be based on the process capability.*

17. What FRCs are included in the excipient specifications?

Answer/Comment: *It should be noted that although some characteristics may be included in the standard sales specification, others, especially physical characteristics may not be.*

IV. Equipment and Production related Questions

Questions from the suppliers

18. Did you identify the process parameters and material attributes that can have an effect on the product CQAs? Are the CQAs influenced by equipment or scale-up operations and can you provide information of the formulation production equipment?

Answer/Comment: *Yes to a certain extent and this should be shared with the suppliers under confidentiality. At first instance, the identification is based on pharmaceutical experience and literature, during development user wants to confirm the potential relationship.*

19. Is the user willing to avoid unnecessarily tight specifications for the excipient as a result of a poorly derived design space or lack of flexibility of manufacturing methodology and not to base requirements on lot selection?

Answer/Comment: *Agreed. The necessary information and samples are needed from the suppliers to avoid this happening. The design space is based on extensive experimentation including the quality of the materials that we have. There may be a number of factors, sometimes competing factors that have impact.*

Questions from the users

20. What is your understanding of critical material parameters (incl parameters which are not on CoA but are known to be functionally relevant) including process control of the excipient?

Answer/Comment: *This topic should form part of the dialogue from Q5 and Q6.*

21. How do you demonstrate that your process is robust, in control and stable?

Answer/Comment: *Most excipient manufacturing processes will be operated within validated process limits and in-process data generated to ensure consistent product*

22. What is your production process capability in terms of expected CQA/FRC variability?

Answer/Comment: *This can be demonstrated by historic process data, but some excipient manufacturers may consider this as sensitive information especially for products where many competitors exist.*

23. Are you willing to engage in rational spec setting process based on process capability (supplier side) and product requirements (user side)?

Answer/Comment: *Most excipient manufacturers will agree to this provided the requirements are in line with material manufactured using the normal production parameters. Any specifications which include limits not normally achieved during standard production or which need to be made using non validated process conditions need to be negotiated commercially.*

V. Supply of samples

Questions from the suppliers

24 How many samples would be needed and what samples are required (at the edges of specifications or extremes)?

Answer/Comment: *This will depend on the phase in which the QbD-experiment is organized and on the final production batch scale and excipient functionality. User and supplier should discuss this at the start of the QbD-activities to have a clear understanding of the project requirements.*

The samples will need to be selected for specified values of the FRC of concern. Typically the values will be specified near the centre, the lower and the upper limit of the FRC-specification, in the assumption that the specification reflects the normal production variation.

25. Is the user willing to work with samples that have been manipulated for certain physical parameters, such as particle size?

Answer/Comment: *This is possible taking into account the following:*

- *the samples should represent material that is or can become commercially available*
- *the user should be informed of the nature of the manipulation*

- *the impact of the manipulation on the QBD-purpose should be negligible according the user*

26. To test FRCs of excipients do you expect to receive material from validated GMP processes?

Answer/Comment: *Not necessarily since the QbD work is done under GLP which is sufficient. If the material is still representative of material manufactured according GMP, then this is acceptable for non-clinical experimental work.*

Questions from the users

27. Can you deliver samples from normal production which varies on the edges on the agreed specification limits related to certain FRCs?

Answer/Comment: *Most excipient suppliers will be willing to supply samples at the edges of normal production ranges. In some cases this can be made easier if the user is willing to work with similar but related grades of the product (eg food grade).*

The users should realise that provision of samples, especially those which are not available 'off the shelf' can be an expensive operation and in some cases may only be provided when the supplier can identify a genuine commercial opportunity.

* Including Certificate of Analysis (CoA), information on compliance and origin (e.g. lab scale/production scale/pilot scale, manufacturing scale)
* Timely supply of appropriate amounts of samples.

Answer/Comment: *Samples at the edges of normal production ranges may take some time to collect as they are produced infrequently and not normally by design. However when collected then should be available quickly. Samples tailor made to a custom specification may take a longer time to produce*

28. Would it be acceptable for you to stress the material outside of a validated process to supply material outside the extremes of the specifications, if required?

Answer/Comment: *Excipient manufacturers do not want to make batches outside of specification, as products are often made in huge batch sizes and there is no market for out of specification material. Products made at pilot scale may not be representative of those made at commercial scale*