# Webinar 1 - Q&A

- How does one bridge API particle size and dissolution to propose CRS outside of clinical experience range for API particle size if the mfg process and disso method profile sees no difference in DP made with larger PSD?

  **Answer:** Clinical relevance means that there's a link between in vivo PK data and in vitro disso. Here it seems you are trying to justify wider API PSD specs. There are many facts to consider since a a disso method may not be sensitive towards API PSD for a highly soluble drug or if during the manufacturing process (granulation?) the PSD is changed (i.e., reduced). For ER products, the release mechanism may be so slow compared to intrinsic API dissolution, that your disso method can't see a difference. Ultimately, one should interrogate what drives dissolution in vitro and in vivo (i.e., do tablets or granules with larger or smaller particle distribution show comparable dissolution in BR media, if they are not, do you have sufficient data/information to evaluate PSD in a PBBM?).

- Most of these in vitro dissolution tests are designed to mimic what is happening in an average individual, how to extrapolate the knowledge gained from these in vitro dissolution studies to a population esp. individuals which could be at higher risk of bio-inequivalence?

  **Answer:** There are two elements to this, firstly is API PK different in sub populations which is a clinical pharmacology question and not related to Pharmaceutical Quality and secondly could product performance differ between populations / in individuals. Currently Clinical BE studies are selected in a 'general' population (either HV or General Patient Population) and individual bioequivalence is not considered (individuals could affect the overall result in a BE study depending on the powering of the study). PBPK modelling may provide insight into both these issues, if it was thought that there may be a formulation by individual interaction it would be good to address this at the product design / early QTPP stage so that this is designed out of the final product. The biopharm risk/quality of the API and drug product will affect the likelihood of by individual interactions.

- Are there any known risks of population differences in absorption kinetics that could confound understanding of dissolution performance and clinically relevant dissolution?

  **Answer:** Please see comments about individual vs population BE above, it is well known that patients may have changes in GI physiology that can impact drug absorption, such as GI surgery, and changes in motility. Again, the impact of these factors could be probed using PBPK modelling. If a particularly patient characteristic is prevalent in the population to be treated it would be desirable to design the drug product to account for this characteristic and still perform well.

- BCS Class 2 API - one or two point DP disso spec for IR capsule - what is the expectation?

  **Answer:** Assuming the method has adequate sensitivity towards CPPs and CMAs that could impact bioperformance, and if in vitro dissolution is complete within 45 min, I would suggest 1 dissolution timepoint. There are incidents where 2 dissolution timepoints are required: one early timepoint to probe the rate is within clinical experience and a second one to probe polymorphism. I hope we can debate this at a future meeting.

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- What about the other (non compression driven) causes of slower dissolution profiles (granules/api properties) : does it also translate into in vivo assessment, which in this case would inflate the clinical studies?

  **Answer:** Yes, if you have multiple factors that impact in vivo performance you should consider testing them. However, would suggest a rigorous biopharm risk and process risk assessment first so that you can narrow down the factors you really need to study.

- Pertaining to the establishment of a safe space: In case the in vitro QC method is 'over-discriminating' a certain CMA or CPP (not relevant in vivo), can those in vivo data help to justify the envisaged QC method by setting broad specification to allow releasing slowly dissolving, but bioequivalent acceptable batches?

  **Answer:** Yes, if the CMA/CPP is driving dissolution, then in my opinion- the in vivo data can be used to justify wider specs. This seems consistent with the EMA 2017 reflection paper and other guidance.

- What about ingredients that have no impact on dissolution profile but have impact on bioavailability?

  **Answer:** The functionality of each excipient should be understood (= outcome of the Biopharm Risk assessment). In my opinion, the removal or addition of a small amount of non-functional excipients, preservative, etc is unlikely to affect clinical performance but this should be assessed on a product-by-product basis. However certain changes in for example Permeability Enhancers are expected to change bioavailability. The latter cannot be controlled via a CRDS and meaningful changes should be evaluated in a BE study. Generally, to date CRDS are limited to a qualitatively and in many cases quantitatively fixed compositions.

- In the presentation it was mentioned that the development was start with biorelevant disso and then move to QC disso which seems to be conventional method but still don't know whether if it is clinical relevant until we do the IVVIC after into human? Any example using biorelevant disso as clinical disso?

  **Answer:** A biorelevant method is not necessarily clinically relevant until a link to in vivo performance has been shown. Many companies are using their diverse BR disso methods internally to gauge biopharmaceutics risk in development and for changes post-approval but they do not share this with agencies. I also have not seen or heard of a company filing a BR disso method in an IND/IMPD to release clinical trial materials. If and how BR disso is used in the development space and how this information can be shared at the IMPD or market application stage to enable efficient life cycle management is a great topic for future meetings

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- When performing an in vivo study with the aim to establish a dissolution safe space, is it necessary that the 90% confidence intervals are within the bioequivalence criteria? If yes, these clinical trials may need to be powered extensively, and may significantly increase costs. Or can the GMR alone also support building a safe space?

  **Answer:** Great question….I personally think that demonstrating BE based on PK is overkill especially for clinical relevance. Companies need to know what drives safety and efficacy. For example, if Cmax is important from a safety perspective and there is evidence that if Cmax within a GMR ration of let's say 0.7 and 1.35 (90 % CI) is safe for patients, then that wider range may be fine. I personally think if you run an experiment you should report the confidence interval. These wider ranges –when justified- should significantly increase Power (and lower the number of subjects thus making the study manageable). It would be great to have a discussion of how to study multiple Biopharm risk factors and what acceptance criteria to apply. Otherwise, companies won't invest in developing appropriately discriminating dissolution methods - which I think is the bigger risk for patients.

- What about HA acceptance (and differences between different HAs) of the examples shown in the presentation (towards broad specs, going beyond f2...)?

  **Answer:** These products were approved in only a few markets. The first example was showcased many times by FDA and wider specs were approved in other markets. The second example was only filed in Japan and they reviewed the spec proposal favorably.

- How do we justify to our medical and clinical colleagues (particularly outside large pharma) that running PK studies for safe space purposes in late-stage CMC is a risk-free strategy for the NDA?

  **Answer:** running a BE study always carries some risks (1-power). This should be weighed against the risk of having a product on the market that fails release specs or requires unnecessary tight controls (and of course releasing product that is not performing as intended using poor control strategies). This is not only a struggle for small companies where resources are tight. From what I learnt over the years, it seems that justifying these studies in companies that share accountability for product quality across divisions is easier than for companies where development and manufacturing are disconnected.