Drying Modeling RFP Q&A – Updated August 14, 2020

- **Does the Availability Requirements outlined in 2.3.2 imply that I need to turn my in-house code into a sellable product *or* I need to team up with a commercial software company (e.g. like EDEM for DEM modeling) in responding to the proposal in order to have their sellable product include my advances which meet the required features as outlined in the RFP? Or instead is it acceptable to establish a mechanism for ETC participants to access an executable version of my code as an alternative?** *It would be preferred to have the in-house code available as a commercial product, but it is acceptable to provide access to an executable version of your code.*

- **For our proposal we will evaluate alternatives to ball milling and RAM mixing for attrition characterization and modeling would be mechanical models of single particles breaking along fracture planes and attrition from single particles.**
    - **Is what we are proposing sufficiently differentiated or complimentary to be interesting to you?** *Yes, the approach you have summarized would be of interest. ETC will need to consider how it fits into the scope of our current RFP, but we are interested in the fundamental attrition work.*
    - **Are proposals that do not involve DEM per se considered?** *It is fine to submit proposals that do not involve DEM. We are open to alternative approaches on understanding this issue.*

- **We assume the dryer design is a typical agitated filter dryer. Is there any other specific dryer type of interest?** *Yes, the dryers of interest would typically be dryers with contact agitators (e.g. conical, filter-dryer etc).*

- **Future extension of project can be developed for fluidized bed dryer or similar equipment where a fluid flow also need to be simulated by CFD-DEM.** *At this time, fluid flow type dryers are out of scope. Our current interest in focused on drying of APIs and drug substance intermediates.*

- **We assume all materials are crystalline and solvent/moisture is mostly in free form (i.e. the amount of solvent inside the particles (like solvate form) is low), although, we will include a diffusion term in our model to take this limited value to the account. Do you agree with this assumption, or do you expect to have significant amount of internal moisture?** *We agree with the above assumption as a start. As this work progresses, we will also want to consider hydrated and solvated materials as well. For instance, what do we learn about the impacts of dehydration/desolvation on attrition?*

- **Is collaboration with an equipment manufacturer required for the proposal?** *It is preferred, but not necessary for our consideration. A "Letter of Support" from an equipment manufacture is not required nor expected to accompany your proposal.*

- **We would need CAD models or geometry data of the equipment, which also can be provided by ETC. Is such kind of data available or we should work with an equipment vendor?** *These types of data are not available at this time. We will work with the selected respondent to gather any necessary CAD models or geometry data of the equipment.*

- **Based on the literature, a solvent content range of 20-40% would significantly contribute to agglomeration. Is there any data on solvent content threshold, which could be achieved by vacuum filter, for a typical API drying?** *Normally, drying protocols are designed to avoid agglomeration. This is typically done by static drying of the batch until the solvent content range is below the threshold for agglomeration. Once the desired solvent content is reached, the batch is agitated. Our main interest is understanding the attrition of the powder during this agitated phase of drying*

- **We assume the ETC members have their own licenses to process development software and we are not responsible for providing such. Do you agree with this assumption?** *Yes, that assumption is correct.*

- **The deliverable model will be based on DoE and available data during the development phase. A hypothetical future case with significant difference in equipment data or material properties should be simulated, and model and database should be updated (model life cycle management). In this case, the future revision/update would cost new computational resources and time, which will be billed separately during the 3 years of post-project. Do you agree with this approach?** *We would request that you outline this in the RFP. We cannot make this commitment until we review the full RFP. Please note that ETC projects are fixed duration projects meant to facilitate the creation of new technologies. The optimal goal of any ETC project is the project output becoming a commercial product offered and supported by a vendor so it is available to the greater scientific community.*

- **The computational resources (CPU and GPU) and simulation run time on HPC is responsible for the most of the project cost. We expect a multidimensional DoE and model setup by around 200 cases for different materials and equipment and process parameters combination will be required. Is there a baseline for number of cases and what is your strategy to compare proposals' cost vs extensivity of activities?** *ETC hasn't established a baseline for the number of cases. We recommend respondents explain their full rationale in the RFP. As for comparing similar proposals, we will follow-up with questions to respondents with further questions to clarify.*

- **What are the requirements with respect to physical properties? Are there particular thermodynamic models that need to be considered and if so, which property packages do ETC members use for this purpose?** *Our main concern is the impact that agitated drying has on particle size, especially formation of fines. Currently, this development work is mostly done empirically.*

- **As regards DEM interfaces, which DEM tools/packages are used by the ETC members?** *Currently, the approach used by most ETC members to study attrition is done empirically. Due to the complexity of the DEM tools/packages, these are not currently used in current development workflows.*

- **In section 2.2 of the RFP, it is indicated that the phenomena of drying and in particular attrition should be considered within the developed model(s)? Are other mechanisms such as agglomeration also of interest?** *For now, attrition is the main focus of this RFP. We are interested in the agglomeration mechanism for a potential future project.*

- **Are there particular publications that could be implemented that the ETC members have in mind? Aware of the following position paper published by ETC members:** *We have cited a few papers in the ETC publication below that proposes different approaches to attrition. We can provide further documents/literature sources as needed.*

  Conder et al. (2017) "The Pharmaceutical Drying Unit Operation: An Industry Perspective on Advancing the Science and Development Approach for Scale-Up and Technology Transfer", *Org. Process Res. Dev*., 21(3), 420–429

- **Would this RFP involve the only the implementation of existing science and models and/or approaches that are available in the published literature?** *Yes, that would be our preference. We can provide key papers/resources and we are open to other resources you find.*

- **In section 2.2, it is outlined that the developed solution must "have a low barrier to entry". What is meant by this?** *Essentially, we want this product to be readily used by bench scientists to guide experimental development work. Our desire is to have a product that does not require extensive programming/model building expertise to use.*

- **In section 2.3.1, it is stated that *"Must be able to replicate attrition behavior at lab scale (10-50 g) through commercial scale (~100 kg)".* What is meant by replicate in this instance, should a model be able to prediction attrition behavior across these scales of operation in a qualitative (correct directionality) way only or also quantitatively? Is it about complete elimination of experimentation at scale or only reduction of experimentation at scale?** *Ideally, the closer we can get to a quantitative outcome the better. If the tool helps us reduce experimentation or anticipate direction of property change that would be very valuable to us as well.*

- **Requirement in section 2.3.1 "*Must be able to hand a range of pharmaceutical compounds including free forms and salts (hydrochloride salts, etc.)*". What additional requirement does this represent? Do we need to track potential for transformation of the solid form? Is this related to solubility of the solid forms?** *This is meant to show that the final product has utility for several pharmaceutical molecules, as opposed to being validated from only one compound. We wanted to avoid having a product that only "worked" for a model compound but not for real-world compounds.*

- **Data processing requirements indicates that a "range of particle size distributions (PSD) and morphologies should be evaluated." Should the model also provide an indication of how the shape of the particle evolves during the drying process? Is this primarily with respect to needle shaped particles (where you could assume breakage across the length of the particle) or all particle shapes?** *It is preferred that the model account for change in PSD and morphology. We would like this to be applicable for all particle shapes.*

- **In section 2.3.1, it is mentioned that proposal strategies for the validation of developed technologies should be outlined. Are the ETC members also in a position to provide experimental data sets for model validation purposes during the project? What is currently measured in basic & advanced AFD experiments? What other measurements would ETC members be willing to consider if they would improve the predictive capabilities of the model?** *It is not certain if ETC members will be able to share data sets at this time. Typically samples are taken during the drying process and analyzed for particle size/morphology. In some cases, the torque on the agitator is measured during drying. Otherwise, impact on particle size is compared to the drying protocol (e.g. agitation time and frequency) and dryer equipment.*

- **What is the desired duration of the proposed project? Section 2.3.3 suggests a 3 year duration.** *Typically, a 1-2 year timeline is desired.*

- **For section 3, "Demonstrate domain expertise and an ability to work collaboratively with the ETC in development of the spatially resolved spectroscopy probe for application in pharmaceutical drying processes."Can the ETC provide further details on whom is developing these probe(s) and provide further details on what exactly is being sought here? Will the developer of the probe also be a party to this RFP?** *This was an error in the RFP. Please disregard that statement.*