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Questions Received for ETC HT Lipid Nanoparticle Synthesis System RFI (Updated May 31, 2022)

1. Ref Section 2.3.1, what is meant by non-contact dispensing? (e.g., no contact between which system elements?) and what are the drivers for this requirement (e.g., zero cross contamination)?
    - **ANSWER**: The main consideration for this requirement is zero cross contamination across different lipid stock solutions. Another consideration of the automatic non-contact dispending system is to minimize manual labor/error as much as possible.
2. Are alternatives to non-contact dispensing potentially acceptable if they meet technical requirements in areas such as zero cross-contamination etc.?
    - **ANSWER**: Alternatives to non-contact dispensing could be considered as long as the zero cross contamination main consideration is respected.
3. Is the 0.1ml lower target on sample size the total volume of lipid solution that is to be used, or the total of lipid solution plus aqueous (payload) solution?
    - **ANSWER**: 0.1 mL will correspond to the lipid phase itself. It is not including the aqueous phase.
4. The requirement specifies "preparation of >20 LNPs at a time". Are sequential or hybrid parallel/ sequential approaches to generating samples acceptable if processing time is acceptable and other benefits are realized?
    - **ANSWER**: Ideally the system would prepare as many LNP formulations as possible in parallel but a hybrid system could be considered. For example, if the system can prepare 4 LNPs in parallel, a system that can automatically switch to next sequence of 4 LNPs will be preferred. If preparation in parallel cannot be achieved, we will consider automatic system that can prepare LNPs sequentially.
5. Are there any guidelines on desired throughput, e.g., number of samples required per day?
    - **ANSWER**: Our recommendation would be 20- 100 formulations a day. Our main considerations will be the processing time per formulation and the reproducibility.
6. Lipid formulations used to generate LNP are typically comprised of 4 or more components. Are these to be combined prior to loading onto the system or loaded onto the system separately and mixed at the time each sample is processed?
    - **ANSWER**: We would like the lipid formulations to be loaded onto the system separately and mixed at the time each sample is processed. If the automated system can handle stock lipid preparation that would be the best since the majority of time is spent on preparing stock lipid solution.

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7. Is it acceptable for wetted parts of the system to be washed and reused (if performance targets are met), or must they to be single use?
    - **ANSWER**: Single use cartridges would be preferred to avoid cross contaminations and lipid precipitation but if criteria are met, we are not excluding parts of the system to be washed and reused. An automatic qualified washing will have to be included and we will have to assess the need of quantifying residual solvent.
8. Are there any guidelines on the max/min flow rate and flow rate ratios that are required/ desirable?
    - **ANSWER**: We leave this question open depending on the vendors capacities in order to achieve reproducible MPs formulations.
9. Ref Section 2.2, is "a pressure driven system" a requirement , or just desired?
    - **ANSWER**: "Pressure driven system" would be preferred but we are open to other systems if the vendor can prove they can provide uniformly distributed motor force to the aqueous/organic phases and overcome dead volume.
10. Are there any general guidelines for desired project completion timelines and costs?
    - **ANSWER**: The funding available for projects is not determined up front. Respondents should estimate the cost of the project and the total funding sought from ETC. Historically ETC funding has been in the $0 - $400,000 range but there is no hard limit on the amount of funding. Once a project is scoped out and a Statement of Work available, the ETC members will determine if there is sufficient interest to fund a particular project and meet the requested funding amount. As mentioned in Section 5.4 of the RFI, the funding provided by ETC to a commercial vendor should be considered seed funding to supplement the total development costs, with the collaboration investing as well.

      The project duration should be proposed by the 3rd party, based upon the time they believe they need to complete the project. Projects in ETC typically last 1-3 years with options to execute additional work through new SOWs after the completion of the initial SOW.

11. For the high level requirements, did the ETC also gather requirements from small and mid sized pharma and biotech? Or are the requirements determined for only large pharmaceutical companies like the ones on the ETC?
    - **ANSWER**: Currently, requirements are coming from ETC members listed in the RFI section 2.1. If you have additional requirements gathered from your interactions with non-ETC members, we be willing to consider these as well or find an appropriate mechanism to gather additional requirements from non-ETC member companies.
12. What is the desired number of samples run per day? Per week?

- **ANSWER**: Our recommendation would be 20-100 formulations a day.

13. Are there any sampling, analytics or purification steps to be included within, or to be compatible with, the workflow?
    - **ANSWER**: Currently, sampling after NPs formulation is no included in the scope of the work but if the vendors have the capability, it would be a nice to have. Similarly, purification and analytics are not in the scope but could be desired.
14. Are there any criteria used to evaluate the project that is more important than others? For example, project timelines, project cost, level of support needed, technical expertise, company experience.
    - **ANSWER**: Cost and technical expertise of the collaborator are the most important criteria.