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The following are the responses to all of the questions received regarding Portable NMR Reaction Monitoring Platform.

1. **I'm curious as to the choice of field strength (60-200 MHz); is the expectation that the chosen solution will be a permanent-magnet based system? There doesn't appear to be much emphasis on magnet specification in the project description in which case a superconducting magnet offering might be at a disadvantage?**
    - ANSWER: The project is not limited to a permanent-magnet based system, so a superconducting magnet is also welcome as long as it meets the following specifications: 1. The footprint is sufficiently compact to fit in a fume hood. 2. It's portable, and 3. It does not need special utilities (electrical, cryogens, etc.) requirements & support, i.e. it should be compatible with electrical voltage standard 120V or 208V US, and does not need cryogens, etc.
2. **We discovered your project for a portable NMR reaction monitoring platform and was hoping you could clarify the timeline for me. I interpret this document to say only the questions we have on the specification are due on April 11th, clarification on these questions will be submitted by April 25th and with these answers our finalized project proposal in this filalble PDF is due on May 9th. Did I interpret that correctly?**
    - ANSWER: Your interpretation is correct. We are asking people to submit any questions they have to ETC by April 11. All questions received will be discussed with the team and answers provided back by April 25. All questions received will be anonymized and posted on the project page of our website (https://www.etconsortium.org/portablenmr) so everyone can benefit from the information. The deadline for responses is May 9. The fillable form has been provided to aid in your response but feel free to include any additional documents to support your response as well.
3. **Is it possible to apply for the project with an analytical tool that is not NMR such as MRR (Molecular Rotational Resonance)?**
    - ANSWER: While the RFI requests an NMR-based tool, if you feel that use of the complementary technique MRR will satisfy the user requirements specified in the RFI, ETC would welcome your response.
4. **What is the range in cost available for the project?**
    - 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.

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5. **Given the indicated range for desired field strength (60-200 MHz), is the expectation that the chosen solution will most likely be a permanent-magnet based system? There isn't much emphasis on magnet specification in the project description in which case a superconducting magnet (say 200 or even 300 MHz) offering might be at a disadvantage even if sufficiently compact to fit in a fumehood as desired?**
    - ANSWER: The project is not limited to a permanent-magnet based system, so a superconducting magnet is also welcome as long as it meets the following specifications: 1. The footprint is sufficiently compact to fit in a fume hood. 2. It's portable, and 3. It does not need special utilities (electrical, cryogens, etc.) requirements & support, i.e. it should be compatible with electrical voltage standard 120V or 208V US, and does not need cryogens, etc.
6. **We have a proven 400 MHz liquid-cryogen-free magnet technology for reaction monitoring and based on the success of that system we would like to respond to the RFI but currently lack formal partnerships with NMR specialists to give an adequate response; is it possible that the ETC may look to connect providers who, together, could provide an enhanced solution?**
    - ANSWER: Yes, connecting providers who responded to the RFI is something ETC could decide to do if the ETC team felt a better solution could be achieved with multiple respondents working together. In the event ETC does wish to explore engaging multiple respondents, the ETC Secretariat will ask each respondent individually if they would be open to consider a working with another respondent to develop a joint proposal. This is strictly voluntary - i.e., the respondents can choose not to work with another respondent on this project. If both respondents are willing to consider this approach, ETC will facilitate the introduction and ask the respondents to come back to ETC when they are ready with their joint proposal. Alternatively, it may be easier for you to identify a collaborator you wish to work with and submit a joint proposal.
7. **As we are potential suppliers for the data analysis part of this analyzer system (but NOT the hardware!), I would just like to make sure I correctly understand what needs to be done for contributing. Could you please indicate how to best proceed?**
    - ANSWER: ETC team would be interested in learning about options from the hardware and software side. In the past, software vendors have partnered with hardware vendors and done a joint proposal. Other times, ETC has explored with respondents based upon their individual proposals their willingness to work together and develop a joint proposal.
8. **What is the expected budget for this project?**
    - 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.

9. **What is the expected level of post project solution uptake?**
    - ANSWER: ETC does not have insight into the information you are requesting, as this is considered market research and something that is outside our scope of activities. The members of ETC who are participating in this project (listed in Section 2.1 of the RFI document) are the companies that are interested in this project and would be potential customers of the commercial solution.
10. **Is it intended that the selected partner should supply a development instrument to the consortium? If this is the case, where would this instrument be situated?**
    - ANSWER: Yes, a development instrument to allow ETC members on the project to test and evaluate the technology will likely be needed. Making the instrument available to ETC members for testing can occur in several ways: 1) shipped and setup onsite at the each of the various companies; 2) setup in regional locations allowing companies to come onsite to test; or 3) system setup at your facility for ETC members to test onsite or send samples for testing.
11. **What confidentiality clauses will be put in places to prevent any risk of any details of a bidder's information being communicated with other bidders?**
    - ANSWER: Please see section 1.3 in the RFI which states that "*Responses to RFI should contain only high-level discussions of product development efforts and should not contain trade secrets or confidential information. ETC does not make any confidentiality commitments with respect to RFI responses but agrees not to publicly distribute RFI responses outside of ETC or share RFI responses with other respondents*."
12. **What confidentiality clauses will be put in place to prevent details of the project once it has commenced being shared outside of the consortium members?**
    - ANSWER: For projects done in collaboration with ETC, we typically execute our standard NDA with the 3rd party.
13. **Can you supply the ETC's Development Agreement and Non-Disclosure Agreement accelerator templates please?**
    - ANSWER: These will be supplied to the 3rd party is chosen for the project.
14. **When is the anticipated project start date?**
    - ANSWER: Currently unknown at this time since ETC may decide to scope a project with one of the RFI respondents or issue a more detailed RFP. This RFI process is scheduled to conclude in June 2022.
15. **Can we contract out development of sub systems or work with external experts to facilitate rapid development?**
    - ANSWER: Yes. You can sub-contract out any of the work for a project with ETC. ETC will execute the contract with the 3rd party selected for the project; the 3rd party would be responsible for any delays or issues relating to the subcontracted work.
16. **If the development meets its intended goals, are the techniques developed usable by other vendors?**

- ANSWER: It depends if the developed techniques are considered intellectual property or not. Any IP developed by the collaborator as part of the project will reside with the 3rd party collaborator and it is up to the collaborator to decide how to license this IP unless licensing predetermined during scoping phase and stated in the SOW and/or development agreements. It should be mentioned that ETC in conjunction with the 3rd party collaborator typically publishes the output of projects to peer reviewed journals which will con the techniques used in the project. These manuscripts are reviewed and approved by all parties before submission.

17. **What are the temperature stability requirements in the transfer line and sample cell?**
    - ANSWER: ± 2-3°C.
18. **Is it acceptable for shimming to be done once the system has stabilized at a given target temperature?**
    - ANSWER: yes. Once at the target temperature, re-shimming should be completed in minutes.
19. **Are other X-Nuclei such as 29Si, 7Li, etc. desirable? And is tuning between these nuclei required to be automatic?**
    - ANSWER: nice to have but not required. Automatic tuning would be required for interleaved experiments.
20. **Is cross polarization, decoupling and NOE enhancement desirable?**
    - ANSWER: Yes. As regards decoupling, proton decoupling from ^{31}P & ^{13}C will be desirable.
21. **Can we introduce a compatible reference sample into the system for shimming?**
    - ANSWER: Ideally, we would like to run reactions as close to process conditions as possible. Therefore, no physical mixing with the analyte, a separate sample is acceptable.
22. **What sample is the target SNR requirement specified for?**
    - ANSWER: We would like to use a solution of sucrose in D_2O at a nominal concentration of 1 mg/mL. After filling the flow cell, the pump should be stopped. The sample in the flow cell must be allowed to stabilize for at least 5 minutes.

      Experiment: Single-pulse 1D 1H NMR with 90 degree pulse, full relaxation, and a total of 16 scans. The same spectrum will be used for both S/N and lineshape testing.

      Signal-to-noise (S/N) test: apply LB=1Hz and double the number of data points using zero filling. Measure S/N of sucrose anomeric proton using a noise region of 180 Hz starting 3 ppm downfield from the position of the anomeric proton. Specification for 1H S/N: at least 80:1

      Lineshape test: perform test without applying apodization (no LB). Measure the full width at half height (FWHH) of the sucrose anomeric proton as well as the depth of the splitting.

      Specification for 1H lineshape: FWHH below 5 Hz, and resolve anomeric splitting at half-height.

23. **Software Requirement: "Real time concentration vs time data with the ability to correct in situ any signal drift caused by changes on pH, etc. that might occur during the reaction." Does this refer to change of integration regions and peak picking for data processing? And/or also for acquisition parameters, for example for defining solvent suppression regions.**
    - ANSWER: The statement above is referring to the ability to change integration regions for data processing in cases a signal drift occurs during a run. The ability to change acquisition parameters for defining solvent suppression regions would be required for in-situ real-time monitoring of the kinetic profiles.
24. **Is the ability to interact with additional hardware peripherals through our software required. For example, interfacing with pH, temperature or other peripherals**?
    - ANSWER: Ideally yes. The interface with other PAT tools is highly desirable.
25. **Servicing of the instrument at the user and technician level is possible. Is this desirable?**
    - ANSWER: Absolutely, we would always aim to have the manufacturer provide onsite servicing and be accountable for instrument performance. Ideally, service availability for the instrument should allow next-day or same-week repair throughout US pharmaceutical laboratories; vendor-provided, hardware and software support is expected for the reasonable life of the product. A performance guarantee for 5-7 years is desirable.
26. **Are multiple submissions per vendor allowed? A proposal for a 60 MHz might be significantly different from a proposal for a 200 MHz.**
    - ANSWER: Yes, a vendor can provide multiple submissions if the proposals are significantly different. Each proposal will be reviewed separately and scored on its own merits.
27. **What is the estimated duration of the project?**
    - ANSWER: 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.
28. **Is the selected project going to be funded by ETC? and if so, what proportion of the total costs?**
    - ANSWER: There is no guarantee that ETC will fund any given project. Once a project is scoped out and a Statement of Work created by the selected 3rd party, the ETC members will determine if there is sufficient interest to fund a particular project and meet the requested funding amount. As for the proportion of the total costs, there is no predefined fraction. 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. It is up to the 3rd party collaborator to determine how much funding to seek from ETC.
29. **Does the whole system need to be inside the fume hood? (e.g., is it acceptable to have electronics, amplifiers, etc. in a separate area?)**
    - ANSWER: The electronics, and amplifiers can be outside the hood, as long as it's compact enough to be compatible with a typical lab environment and the system is portable.

30. **Does the system need to fit inside a bench fume hood or a walk-in type of fume hood? What are the minimum dimensions of the fume hood? (i.e., maximum acceptable instrument footprint)**
    - ANSWER: Ideally, the instrument needs to be able to fit inside a bench fume hood so it could be widely adopted in an std lab environment. The walk-in type of fume hood is less common and adds additional facility requirements for some laboratories, again, it's critical that the system can be easily moved when needed. Ideally, both the weight and size should not limit us from placing the system inside of an std fume hood.
31. **What are the requirements or restrictions on electrical power, water cooling, mass of individual components?**
    - ANSWER**:** The system should not need special utilities and facilities (electrical, cryogens, etc.) requirements & support, i.e. it should be compatible with electrical voltage standard 120V or 208V US, and does not need cryogens, etc.
32. **Is the system for a development laboratory, for the pilot plant or manufacturing plant?**
    - ANSWER: The system is intended for a development laboratory.
33. **Should the system/s be for both development and manufacturing, do the hardware system components need to be the same for the development lab and manufacturing plant?**
    - ANSWER: The system is intended for a development laboratory.
34. **What is high pressure? (i.e., what is the minimum pressure the system must withstand?)**
    - ANSWER: Nice to have whatever is tolerated. This solution is not intended for high pressure reactions (for example, hydrogenation and hydroformylation) in the flow cell. It would be nice to handle some sort of pressure, and ideally, we would like the pressure to be consistent throughout.
35. **What are the typical durations of the reactions?**
    - ANSWER: ~10 – 30 min (i.e. Grignard reaction) in the lower end. The upper limit could be anything, from several hours to a couple of days.
36. **How often does the system need to be moved?**
    - ANSWER: The system must be portable, meaning that it could be moved when needed, but the system is not intended to be moved very often. After the move, the system should be able to stabilize quickly.
37. **How often will the temperature of the system be changed?**
    - ANSWER: The ability to change the temperature during the same reaction run is desirable (i.e., for feedback loop automatic optimization of the reaction temperature, or single kinetic run and get the activation energy by changing the temperature over time).
      Question: how fast we can change the temperature, i.e. 10 °C, equilibrate and reshim?
38. **How fast needs to be the temperature equilibration step? (i.e., seconds, minutes, hours, or days)?**
    - ANSWER: Minutes

39. **What is the required temperature stability?**
    - ANSWER: ± 2-3°C. Temperature stability is crucial to reaction rate and shimming.
40. **What is the maximum acceptable clean-up/system wash time?**
    - ANSWER: The purpose of the platform is for reaction monitoring, so clean-up/system wash is only required after the reaction completion.
41. **Is solvent suppression required/important and if so, is the specification of line shape at 0.55 and 0.11% of interest?**
    - ANSWER: yes, solvent suppression (i.e. the ability to suppress multiple signals) is a must to have.
42. **What are the service and support requirements (i.e., acceptable time to response and time to fix)?**
    - ANSWER: Service availability for the instrument should allow next-day or same-week repair throughout US pharmaceutical laboratories; vendor-provided, hardware and software support is expected for the reasonable life of the product. A performance guarantee for 5-7 years is desirable.
43. **What are the requirements in terms of system certification? (i.e., is NRTL approval, UL certification or any other certification required? And if so, are these certifications required for the system as a whole or for the parts of the system?)**
    - ANSWER: A commercial system should process all necessary certifications for use in an industrial laboratory in multiple regions, including North America and Europe. As such, NRTL approval (from labs such as UL, FM, CSA, TUV SUD etc.) for use in North America, as well as CE or similar in Europe is a requirement of the device.
44. **Sensitivity specification is rather vague – can the listed SNR spec of 400-500:1 be clarified. The mention of seeing impurities in 1 scan – what is the minimum concentration of impurities that are expected to be observed?**
    - ANSWER: We would like to use a solution of sucrose in D_2O at a nominal concentration of 1 mg/mL. After filling the flow cell, the pump should be stopped. The sample in the flow cell must be allowed to stabilize for at least 5 minutes.

      Experiment: Single-pulse 1D 1H NMR with 90 degree pulse, full relaxation, and a total of 16 scans. The same spectrum will be used for both S/N and lineshape testing.

      Signal-to-noise (S/N) test: apply LB=1Hz and double the number of data points using zero filling. Measure S/N of sucrose anomeric proton using a noise region of 180 Hz starting 3 ppm downfield from the position of the anomeric proton.Specification for 1H S/N: at least 80:1

      Lineshape test: perform test without applying apodization (no LB). Measure the full width at half height (FWHH) of the sucrose anomeric proton as well as the depth of the splitting.

      Specification for 1H lineshape: FWHH below 5 Hz, and resolve anomeric splitting at half-height.

45. **Is this reaction monitoring platform required to be compatible with both flow chemistry and batch chemistry?**
    - ANSWER: yes, we would like the platform to be applicable for both flow and batch chemistry.
46. **What is the range of reaction lengths that will be monitored? e.g., 5 min – 25 hours?**
    - ANSWER: ~10 min (i.e. Grignard reaction) in the lower end. The upper limit could be anything, from several hours to a couple of days.
47. **What scale of reactions are we looking at? Large process scale or small microscale?**
    - ANSWER: 2-3 mL reaction scale to 1-2 L.
48. **What is the maximum desired data rate (e.g., in concentration measurements per minute)? How long is the typical reaction time we will be looking at?**
    - ANSWER: ~5 seconds/data point in the lower end to tolerate faster reactions (i.e. 5 -10 min).
    - ~10 min (i.e. Grignard reaction) in the lower end. The upper limit could be anything, from several hours to a couple of days.
49. **pH range 0-12 is wide especially given the temperature range. Could there be different solutions and flow-cells at different pHs?**
    - ANSWER: Flow-cells at both low and high pHs are acceptable. This will affect not only the flow cell but other components of the system (for instance, tubing used in transfer lines and pump selection). The tubing/transfer lines should be chemically inert.
50. **Is that pH range required for the entire stated temperature range?**
    - ANSWER: yes. Also, flow-cells at both low and high pHs are acceptable. This will affect not only the flow cell but other components of the system (for instance, tubing used in transfer lines and pump selection). The tubing/transfer lines should be chemically inert.
51. **What is the specification for pressure in cell? Can this be reduced throughout the sample handling or should it be maintained?**
    - ANSWER: This solution is not intended for high-pressure reactions (for example, hydrogenation and hydroformylation) in the flow cell. It would be nice to handle some sort of pressure. Ideally, we would like the pressure to be consistent throughout.
52. **Is there a specified range of viscosities the system must be compatible with?**
    - ANSWER: the system should be able to handle both organic and aqueous solutions.
53. **Must the solution be compatible with all solvents? Which will be the main ones?**
    - ANSWER: The system should be compatible with the most common solvents such as THF, DMF, MeCN, DMSO, Water, dioxane, dioxolane, amines, acetone, CPME, DCM, DCE, etc.
54. **Is the vision for stopped flow or continuous flow when monitoring the rection? If continuous, how fast a flow rate must be supported?**
    - ANSWER: Preferably, the system should provide flexibility to operate in either stopped-flow (stopped-flow should be synchronized through software) or continuous flow mode. However, continuous flow mode only should be acceptable.

55. **Will this be a dedicated online reaction monitoring device or should it also be compatible with static NMR tubes?**
    - ANSWER: Although the main use of the system will be a dedicated online reaction monitoring device, we would also like for the system to be compatible with static NMR tubes, when needed.
56. **Is there a preference for a top-top flow cell or bottom-to-top flow cell?**
    - ANSWER: Bottom-to-top flow cell
57. **Are there any specific lock requirements? Is 19F a suitable lock nuclei for an external lock?**
    - ANSWER: An external lock reference is preferred. Lock using proton signals will be valuable.
58. **Protonated lock – does this imply that there is a consistent proton reference or simply that deuterated solvents will not be used?**
    - ANSWER: Deuterated solvents could be used, but the system is mainly intended for no-D NMR applications.
59. **What service/maintenance is acceptable?**
    - ANSWER: Service availability for the instrument should allow next-day or same-week repair throughout US pharmaceutical laboratories; vendor-provided, hardware and software support is expected for the reasonable life of the product. A performance guarantee for 5-7 years is desirable.
60. **How long must the instrument run without downtime (shimming, maintenance, etc.)?**
    - ANSWER: Reactions typically don't exceed the 2-day threshold, so guaranteeing 40-48 hours of continuous operation without downtime will be ideal.
61. **What kind of magnetic interference can we expect (e.g., magnetic stir plate, vacuum pump etc.)?**
    - ANSWER: yes, magnetic stir plate, vacuum pump, Easymax instruments, PAT tools such FTIR, Raman, etc.
62. **Is decoupling required? If so, which nuclei are required?**
    - ANSWER: yes, proton decoupling from ^{31}P & ^{13}C will be desirable
63. **Does the spectrometer have to observe all listed nuclei simultaneously or would different solutions for different reactions be possible, i.e., one instrument or several can meet these specifications? Single channel? Dual channel? How many simultaneous channels are required?**
    - ANSWER: yes, one single system should observe 1H, 19F, 31P, and 13C. Other nuclei are nice-to-have. We require simultaneously tuned 1 high band and 1 low band channel.
64. **Does probe require dual channel 1H-19F and the 19F channel eventually tunable to 31P/11B/13C but keeping a 1H channel independent? Or single channel tunable from 1H–19F–11B-31P and 13C.**
    - ANSWER: yes, one single system should observe 1H, 19F, 31P, and 13C. Other nuclei are nice-to-have. We require simultaneously tuned 1 high band and 1 low band channel.

65. **What degree of manual tuning is acceptable? For example, difference between aqueous and organic solutions?**
    - ANSWER: automatic tuning is required.
66. **Is there a desired 90 pulse times? This could have an impact on the system configuration and power requirements.**
    - ANSWER: ^{1}H pulse of not more than 25 μs.
67. **Any data integrity requirements? GxP, IQ/OQ, Part 11? ELN requirements?**
    - ANSWER: No GxP/IQ/OQ and ELN requirements at this point.
68. **To be done onboard or in remote computer?**
    - ANSWER: Both. The instrument should be connected to the company's network so it can be controlled remotely with software.
69. **Realtime connectivity to influence NMR operations or just output jdx files?**
    - ANSWER: Both, real-time connectivity for in situ reaction monitoring, and jdx or other formats must be available for more in-depth data analysis of the reaction(s).
70. **What data analysis and visualizations are required? Is it acceptable to transfer the data to a separate software for some of them?**
    - ANSWER: The NMR software should have all the capabilities of traditional systems that are needed to process and analyze the data. Ideally, some automated processing can be implemented at the instrument. The results of the automated processing (either trend and/or spectra) should be able to be shared in real-time with other software environments (e.g via OPC-UA, Allotrope, or other approaches) where it will be fused with other PAT information.
71. **Is jdx an acceptable "unified and open file format"?**
    - ANSWER: yes
72. **What does "pausing" a queue mean? Does that mean cancel a currently running experiment and re-start it again later, or something else like pause mid-experiment and resume from the scan that it was paused on?**
    - ANSWER: It means that we should be able to pause mid-experiment and resume from the scan that it was paused on.
73. **Will the user interface and security environment need to accommodate users of varying expertise and data- and/or feature-access permissions?**
    - ANSWER: not from a security perspective. From a practical perspective, it would be valuable to have a primary screen that gives accessibility to the most commonly used features. Then an 'advanced' button to allow advanced users to access more sophisticated settings.
74. **How will reaction vessel communicate with the spectrometer? Desired protocol?**
    - ANSWER**:** this can be flexible. OPC-UA is attractive both for control and data exchange. However, other alternatives may be acceptable.

75. **LF Benchtop NMR (60-200 MHz) with a footprint suitable for lab hood – if in a safety case is the lab hood required? Or is this merely meant to highlight the size of the instrument?**
    - ANSWER: Chemicals will be handled, so the system needs to be in a fume hood for safety reasons.
76. **In fumehood or in safety enclosure? Both? Is this explosion proof? Is there a standard or designation that we're trying to meet (e.g., ATEX)?**
    - ANSWER: The primary focus is the development space, and explosion ratings are not a requirement. In the future, if the instrument will be considered for a production environment, then explosion ratings will likely be important, but that's not a critical requirement at this point.
77. **What is the maximum deviation in temperature along the sample line that is acceptable?**
    - ANSWER: ± 2-3°C. Temperature stability is crucial to reaction rate and shimming.
78. **Does a single plumbing package need to handle all requirements? Can there be interchangeable plumbing packages to meet different requirements?**
    - ANSWER: Further clarification on this question might be needed. If the question is, we can use separate devices for a heat exchanger vs. the sample delivery system, then that is acceptable.
79. **Is there a requirement for handling the material after the flow cell? Does it need to be directed somewhere specific, or is it waste? What are the temp control requirements for this material after it is sampled and leaves the flow cell?**
    - ANSWER: In many use cases, we expect the sample to be in a recirculation loop so it will be delivered back into the vessel. Temperature control throughout the entire sample loop is important. In other cases, the sample may go to waste OR to additional instrumentation (e.g., MS, UV, etc.). flexibility is important to us.
80. **If the material becomes waste, do we need a waste management system?**
    - ANSWER: no
81. **More info for flow circuit layout? Do we need bypass loop, safety shut offs, etc.**
    - ANSWER: : This depends a bit on the proposed solution, but safety shut-offs, interlocks, etc. should be considered.
82. **Are there existing examples or use cases of reaction vessels with a pump and filter that would be similar to what is wanted here?**
    - ANSWER: To the best of our knowledge, there is not a universally accepted solution that works for a wide variety of reaction conditions (high temp, low temp, heterogeneous solid/liquid, heterogeneous liquid/liquid, organic solvents, etc.) that we are proposing.
83. **Will a control of pressure in the flow cell be required (i.e., Have the measured sample be at the same pressure as the reaction vessel)?**
    - ANSWER: yes, the pressure throughout the system should be consistent.
84. **Target size, weight, cost of solution provided?**

- ANSWER: Ideally, both the weight and size should not limit us from placing the system inside of std fume hood. Historically ETC funding has been in the $0 - $400,000 range but there is no hard limit on the amount of funding.

85. **Is a multi-box solution acceptable, where the shielded magnet, probe, and minimal electronics are in the fume hood / enclosure and the remainder is remote? Can the magnet, electronics, VT unit etc. be separate to allow the size of the package that is in the process area to be minimally sized?**
    - ANSWER: yes
86. **Monitor required?**
    - ANSWER: yes
87. **How fast must we be able to change and stabilize temperature of the solution in the flow system? Do we need to change temp actively during experiments? This question applies for controlled temperature changes in the reaction vessel and also controlled changes in the flow cell (by VT system)**
    - ANSWER: The ability to change the temperature during the same reaction run is desirable (i.e., for feedback loop automatic optimization of the reaction temperature, or single kinetic run and get the activation energy by changing the temperature over time). Temperature change/equilibrate/reshim cycle should be done in order of minutes for optimal results.
88. **Do we need a fixed flow cell or interchangeable flow cells?**
    - ANSWER**:** interchangeable flow cell is preferred.
89. **What are the precision specs for vessel temperature control and VT (spectrometer) temperature control?**
    - ANSWER: ± 2-3°C. Temperature stability is crucial to reaction rate and shimming.
90. **Ambient temperature range inside the fume hood / enclosure?**
    - ANSWER: yes
91. **Is there an estimate of the monetary resources that ETC might apply to this project?**
    - 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.
92. **The RFI refers to a "Portable" NMR reaction monitoring platform; however there are no requirements for size and weight of the system. Can you please clarify the meaning of "portable" in this project?**

- ANSWER: The system is not intended to be moved very often, but it must be portable, meaning that it could be moved when needed. Therefore, It is primordial that it does not need special utilities and facilities (electrical, cryogens, etc.) requirements & support. i.e. the instrument needs to be able to fit inside a bench fume hood so it could be widely adopted in an std lab environment. The walk-in type of fume hood is less common and adds additional facility requirements for some laboratories. Similarly, both the weight and size should not limit us from moving the instrument and placing the system inside of an std fume hood.

93. **How does ETC envision the deployment and adoption of this solution after completion of a successful project?**
    - ANSWER: The general intent for every ETC project is that the output eventually results in a new commercial product offering to the scientific community. Through collaboration with multiple ETC members providing collective requirements and feedback to the 3rd party collaborator the goal is that the resulting technology will be fit for purpose and readily adoptable by the industry.

94. **Can individual project sponsors collaborate with commercial vendors in this project?**
    - ANSWER: Individual project sponsors (i.e., members of ETC) are welcome to collaborate with commercial vendors outside of ETC if they so choose to. However, for an ETC-sponsored project, it is expected that all participants of the project working with the vendor are ETC members. Note, the benefits for conducting a project within ETC vs. multiple, individual project sponsors include: collective requirements, single development agreement vs. multi-party agreement, sponsor funding dollars go farther since costs are split over multiple sponsors.

95. **Can you clarify how the NMR specifications for Sensitivity and resolution will be evaluated in this project? Is the plan to use NMR standards and protocols?**
    - ANSWER: We would like to use a solution of sucrose in D_2O at a nominal concentration of 1 mg/mL. After filling the flow cell, the pump should be stopped. The sample in the flow cell must be allowed to stabilize for at least 5 minutes.

      Experiment: Single-pulse 1D 1H NMR with 90 degree pulse, full relaxation, and a total of 16 scans. The same spectrum will be used for both S/N and lineshape testing.

      Signal-to-noise (S/N) test: apply LB=1Hz and double the number of data points using zero filling. Measure S/N of sucrose anomeric proton using a noise region of 180 Hz starting 3 ppm downfield from the position of the anomeric proton.Specification for 1H S/N: at least 80:1

      Lineshape test: perform test without applying apodization (no LB). Measure the full width at half height (FWHH) of the sucrose anomeric proton as well as the depth of the splitting.

      Specification for 1H lineshape: FWHH below 5 Hz, and resolve anomeric splitting at half-height.

96. **Considering an NMR sensor for PAT will deal with protonated solvents; are there any requirements for solvent suppression?**
    - ANSWER: yes, solvent suppression is required.