NIPTE The National Institute for Pharmaceutical Technology and Education
Improving quality and lowering costs of pharmaceuticals

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Response to NNMI RFI

The National Institute for Pharmaceutical Technology and Education (NIPTE)

We enthusiastically support the underlying premise of the NNMI initiative that in order for the US to reclaim its leadership in advanced manufacturing, we must as a nation develop and implement long-term strategies that actively engage industry, government and universities in a sustained innovation partnership. The elements of that partnership must include investment in a consistent and substantial fashion in manufacturing education and research, creation of programs that facilitate both innovation and commercialization of advanced manufacturing technologies, and coordination of tax and trade policies to actively support advanced manufacturing for domestic and international markets.

The two most important competitive advantages of the US are that we have both the best university system in the world and a deeply ingrained entrepreneurial spirit that makes creating and growing companies a natural endeavor in a large fraction of our population. Our main disadvantage is that our universities and our small and medium size companies do not collaborate either effectively or easily. While the tendency of universities to over-protect intellectual property is in part to blame, a more critical issue is that after decades of federal neglect, during which funding for manufacturing-related research was close to non-existent, manufacturing-related research lacks academic prestige and engages a relatively small fraction of the university enterprise. In fact, the tenure processes in many leading universities have a built-in bias *against* research dominated by industry sponsorship. A second disadvantage is that there are very few facilities accessible to both industry and university that can serve as demonstration and test bed sites where advanced manufacturing innovations can undergo the test, improvement and validation cycle at a scale relevant to industrial practice. An associated disadvantage is the lack of hands on education/training facilities in which industry and universities can collaborate in the development of the essential workforce. Such facilities are expensive for universities to build and maintain at the state of the art and to operate in terms of staffing and materials. More so even than space, the total cost associated with professional staff at the knowledge and experience level needed for such facilities simply makes stable staffing infeasible for universities.

Thus, an important part of an effective US strategy for growing manufacturing capabilities is to develop and implement infrastructure that removes the difficulties to academic/industrial collaboration and leverages and synergizes their respective strengths.

Fortunately, while our strengths and advantages take decades to build, our disadvantages can be overcome relatively quickly. We concur whole-heartedly that the NNMI initiative does offer the promise of addressing the above-mentioned US disadvantages but to realize that promise the ground rules for Institutes must be carefully crafted. Our response to the 21 questions posed at the Cleveland NNMI workshop should be taken in that context.

To provide additional context, the National Institute for Pharmaceutical Technology and Education (NIPTE) is a non-for-profit consortium of 13 leading universities with a commitment to innovation in the pharmaceutical manufacturing sector. NIPTE as a collective and through associated major collaborative efforts such as the NSF ERC on Structured Organic Particulate Systems has strong working relationships both with a range of pharmaceutical companies as well as the FDA. Through these efforts we have individually and as a collective sought to advance pharmaceutical product development and manufacture. We believe these efforts have indeed set the stage for advancing to the scope of an Institute.

Specific RFI response:

1. ***What criteria should be used to select technology focus areas?***

   The criteria should include the following considerations:
   - The focus should be to help an existing high-tech industry become healthier, to flourish and grow beyond its current state
   - Implementation should create new jobs or bring back jobs that have been outsourced
   - The technology implemented should address some of the basic underlying reasons why jobs in that industry are being outsourced
   - The new technology should be such that it would make no economic sense to outsource manufacturing given the advantages offered by that technology. If manufacturing were outsourced, it would make the process and product more expensive or of lesser quality.
   - The new technologies should enable the U.S. industry to make a product of much superior quality that others will have a hard time to match. This is possible with superior instrumentation and automation and on-line quality control.

2. ***What technology focus areas that meet these criteria that would you be willing to co-invest in?***

   The pharmaceutical manufacturing sector, encompassing both small molecule and biologically derived products should be one of the target areas. This sector does match well the criteria listed in (1) above, as detailed in the last section of this document. Moreover, it is a sector in which industry, government and academia would be willing to partner.

3. ***What measures could demonstrate that Institute technology activities assist U.S. manufacturing?***

The real measure of effectiveness would be if the institute can develop and demonstrate solutions to some of the fundamental reasons why the target industry has become less efficient, less productive or more expensive and why that industry prefers to outsource off-shore rather than to manufacture in-house or on-shore. Most companies prefer to outsource to avail themselves of cheaper labor and cheaper capital. Sometimes, outsourcing can occur if the industry is unable to find and hire adequate supply of qualified and trained individuals. If the new technology developed by these institutes can address these drivers for off-shoring, then there would be no incentive to do so. By way of example, the institute's technology activities might focus on on-demand, highly efficient small scale manufacturing which will reduce capital, minimize transportation costs and dramatically reduce inventory costs. Accordingly, a measure of impact on US manufacturing could be comparisons of five year average of off-shoring prior to the Institute to equivalent average after the launching of the Institute.

4. ***What measures could assess the performance and impact of Institutes?***

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The traditional measures for university or national labs-based research (papers published, citations, students graduated/postdoctoral students trained) while important will be insufficient for an advanced manufacturing institute with a translational objective. Additional criteria that are at least as important include:

- Tangible support leveraged from companies, other federal and state funding sources, private donors, and the universities themselves.
- IP disclosed, provisional and full patent applications, patents granted and licensed
- Contributions to increased GDP and improved trade balance
- Actual jobs created
- Creation and growth of small and medium companies,
- Number of industrial members

5. ***What business models would be effective for the Institutes to manage business decisions?***

Preferably an advanced manufacturing institute should operate outside of the regular University bureaucracy. This is important in order to ensure that the institute remains focused on its goals (as opposed to university institutional goals). One obvious solution is to create a non-for-profit entity that acts as the recipient and manager of federal and leveraged funds. This approach also would make a multi-university arrangement more manageable than the typical lead/core partner model used by NSF ERC's and STC's. Such an entity could readily manage multiple arrangements with companies and other sponsors, including a tiered membership

program for its non-competitive component, focused consortia addressing projects sponsored by subsets of the companies, and specific contract driven projects sponsored by a single entity.

6. ***What governance models would be effective for the Institutes to manage governance decisions*****?**

   The Institute would be managed through a non-profit organization that would provide fiscal oversight. A Director, assisted by a Deputy Director for Technology and a Deputy Director for Operations, would lead the Institute. Tactical decisions would be made by an Executive Committee consisting of the above three directors plus the managers of the technology demonstration sites established by the Institute. Potentially there could be 3 or more sites with a focus on specific technologies and shared responsibility for workforce development. Strategic oversight would be provided by a Board of Directors consisting of 5-6 members who would serve 3-year terms and be appointed by the non-profit, independently of the Director and the Executive Committee.

7. ***What membership and participation structure would be effective for the Institutes, such as financial and intellectual property obligations, access and licensing?***

   This is potentially a very complex issue. The institute has competing/conflicting priorities in the IP area. On the one hand, it is desirable to impose minimum restrictions on members for using IP developed by the institute. This is desirable both because it promotes membership growth and because it promotes more rapid adoption of institute technology by member companies. On the other hand, it is desirable to charge fees for the use of institute technology in order to promote and build institute sustainability. A multi-tiered membership program with different IP benefits is likely the structure that offers the most flexibility.

8. ***How should a network of Institutes optimally operate?***

   It is critically important that there be sharing of technology and experience across the Manufacturing Institutes. This can be facilitated by Council of Institute Directors but also needs to occur at the grass roots level. One mechanism would be an annual multi-day conference in which commercialization, technology development and education/training methodologies will be presented and discussed. Additional mechanisms could include focused workshops on specific technology areas and tools, which cut across industry sectors. Joint education and training conferences with groups such as the ASEE would help as a vehicle to not only share best practices but also serve to share curricular materials with university engineering and technology educators. Finally, supplemental funding could be made available to Institutes to seed inter-institute projects.
9. ***What measures could assess effectiveness of Network structure and governa*****nce?**

A number of measures would address this issue, including:

- Conduct periodic reviews and surveys to obtain opinions from the stakeholders, including academic participants as well as member industries.
- Obtain statistics for numbers of students (Ph.D. and Post-doctoral students) graduated and placed. Document both where they obtained their first job and the nature of their first assignment.
- Obtain statistics for patents granted and licensed. Evaluate impact of products/technologies involved.
- Track usage of "Technology Demonstration Sites" and assess value to companies using the facilities.

10. ***How should initial funding co-investments of the Federal government and others be organized by types and proportions?***

The Federal advanced manufacturing funding should be matched with in-kind, facilities and direct financial support from State, local government, industrial and foundation sources. The 1:1 match target seems appropriate providing there is flexibility given in the form in which this can occur and the time window over which the matching metrics are calculated. For instance, facilities assignments and equipment donations should be allowed to be spread over multiple years. Secondment of staff to the Institute should be valued at fully absorbed cost levels, both for full time and part time assignments. In order to provide flexibility to adapt to the path taken by an Institute over its lifetime, it is preferable that there be no fixed proportions to which various categories of cost sharing are held. In order to encourage other federal agencies to become engaged in the Institute work, supplementation of direct Advanced Manufacturing funding with funding from such agencies should be allowed in the cost-sharing accounting.

11. ***What arrangements for co-investment proportions and types could help an Institute become self-sustaining?***

Sustainability would be achieved only if a cohesive technical team with a clearly defined identity and brand emerges after the federal funding period. Sustainability would require multiple funding streams, including industrial membership funds, industrial contracts for specific projects, both by individual companies and by small consortia, fee-for-service work, and sustaining contributions by participating universities and state and local governments and federal agencies that directly benefit from the Institute's efforts. IP related income could well develop to support sustainability. However, it is not likely to provide a major income stream for sustaining the Institute within the first few years after graduation from federal funding.

12. ***What measures could assess progress of an Institute towards being self-sustaining?***

The answer to this question is just the logical projection of the answer to the previous questions. Specifically, the metrics would include actual funding in each of the funding streams enumerated above.

13. ***What actions or conditions could improve how Institute operations support domestic manufacturing facilities while maintaining consistency with our international obligations?***

Membership and the benefits of such membership, including both use of Technology Demonstration Sites and collaborations in Institute consortia and projects, should be restricted to companies who have a significant R&D and manufacturing presence in the Unites States. However, since most large companies are international organizations, the institute should not restrict membership and benefits to organizations having a presence only in the United States. However, benefits for using institute IP in domestic manufacturing sites should be provided, such as providing incentives on licensing fees for IP used for manufacturing sites in the US as well as tax incentives for early adoption, such as beta-testing, of new technologies.

14. ***How should Institutes engage other manufacturing related programs and networks?***

The Network of Institutes should develop high level cooperative research agreements with all such programs that have national scope. Agreements at that level would then open the doors to specific interactions with individual institutes. The individual institutes should partner with all relevant regional manufacturing programs, such as Manufacturing Extension Partnership, especially those within the regions in which the demonstration sites of that institute exist. Given the limited resources available to further advance manufacturing, it is important that cooperation rather than competition be the mode of engagement.

15. ***How should Institutes interact with state and local economic development authorities?***

The institute and/or its regional site should identify the appropriate strategy of their contribution into local economic development and job creation. Depending on the circumstances, the strategy may include assisting local industry by providing technical support, helping to create an environment that will promote entrepreneurship and attract outside companies.

16. ***What measures could assess Institute contributions to long-term national security and competitiveness?***

This can be measured by the Institute's ability to create capability for rapid development, launch and manufacture of devices, vehicles and weapons. An example would be the capability for production of required drugs on a short notice

while providing fast and flexible response to unanticipated changes. That can be achieved by a high level of flexibility of the manufacturing system, robust yet flexible synthetic and formulation manufacturing processes, and robust sourcing capabilities. One assessment approach would be to conduct well-documented benchmarking studies.

17. **How could Institutes support advanced manufacturing workforce development at all educational levels?**

The mechanisms are those outlined in response to question 21

18 How could Institutes ensure that advanced manufacturing workforce development activities address industry needs?

A key component of the institute's mission must be to promote the development of a strong human resource pool that is critical to implementing the new technologies in the field. This means to lead in creating and sustaining a "pipeline" of diverse talent that commences at the undergraduate level and continues throughout graduate, postgraduate, and continuing education, augmenting the available workforce in academia, industry, and government. The Institute would carry out its workforce development mission by engaging university, community college and technical / vocational college partners to deliver jointly developed courses, supported by industry representatives who would serve as guest lecturers and contributors of course content and case studies. These curricular materials would need to be continuous reviewed and updated as technology advances. Given the importance of workforce development, the Institute should have one of the senior staff have ownership of this mission component, guided by a steering committee consisting of members from industry, government and academia.

19 How could Institutes and the NNMI leverage and complement other education and workforce development programs?

The most effective way is for the Institutes to partner with universities and community colleges as well as key professional organizations, such as AIChE, ASME, ACS and ASEE. These partners have the expertise to organize and deliver both degree programs and professional education programs. However, they will need Institute help in creating content that builds on the technologies being commercialized by the Institutes as well as the case studies used to demonstrate that technology. Such partnerships will require coordination at the NNMI level so that courses are developed that draw appropriate technologies and content from multiple Institutes, as appropriate. Moreover, while degree programs clearly will need to be offered within the auspices of individual university/community college partners, certificate programs for professional credentialing will need oversight at the NNMI level so as to have credibility and visibility at the national level.

20 What measures could assess Institute performance and impact on education and workforce development?

Appropriate metrics should include the obvious course participation head counts, degree award totals and certificate award counts. NNMI or individual Institutes will also need to create and administer assessment instruments to survey both participants in NNMI education/programs conducted in partnership with the NNMI entities as well as the employers of program graduates. These surveys can be carried out at 1, 3 and 5 year intervals after individuals complete these programs. The mechanics of such assessment programs are well established and the expertise to execute such programs is readily available within the university/community college community as part of the institutional accreditation process.

21 How might institutes integrate R&D activities and education to best prepare the current and future workforce?

The most effective integration mechanism is learning by doing. This can be achieved through student projects and internships carried out within the context of larger Institute projects. Well-established NSF programs such as the Research Experiences for Undergraduates and the Research Experiences for Teachers could serve to generate stipend support for program participants. Summer experiences for high school students are also effective mechanisms for raising awareness and interest of students in STEM areas and could be particularly appropriate at the demonstration sites of the Institutes. Veterans with suitable technical backgrounds attained while in the military could be quickly retooled in civilian advanced manufacturing technologies so as to be effective employees. Of course, graduate internships and postdoctoral appointments within member companies are also very effective mechanisms for technology transfer from Institute projects to industry.

The Pharmaceutical Manufacturing Institute (PMI)

Drivers: When the NNMI initiative is finalized, NIPTE intends to work with the pharma industry leaders to propose a Pharmaceutical Manufacturing Institute. There are three key drivers for focusing on the US pharmaceutical manufacturing sector:

- Pharmaceutical manufacture, spanning both innovative products and generics, is an important sector of the US economy both because of its economic impact and its critical role in US healthcare.
- The global pharmaceutical industry is undergoing significant disruptive economic changes, which threaten to further diminish the role of the US pharma sector as global leader.
- The slow evolution of traditional pharmaceutical manufacturing technology coupled with recent changes in regulatory climate provides a unique window of opportunity for advanced manufacturing technologies.

Program: The PMI will execute a five-part program consisting of the following substantive components:

- Technology Assessment: Initial and continuing review and identification of high impact translational opportunities which are at the appropriate level of technical development to have economic and workforce impact within a three year time frame.
- Technology Development: Reduction to practice of selected manufacturing innovations including small-scale implementation and confirmation through experimental and modeling studies.
- Technology Demonstration: Manufacturing technology implementation, testing and validation of selected new manufacturing concepts at a scale appropriate to support commercialization.
- Technical Assistance: Technical problem solving and consultation to facilitate the commercialization of innovations which have been demonstrated and validated.
- Workforce Development: Education and hands-on training of practicing professional as well as full time students at all degree levels in these technologies.

Outcomes: The technology transfer program envisioned under PMI offers the possibility of a number of needed and desirable outcomes for all pharma manufacturers, generics and innovators, in the US.

- The cost and quality advantages offered by advanced manufacturing technology will serve as driver for the on-shoring of significant levels of pharmaceutical manufacturing back to the US.
- This technology along with the education and training programs offered by the Institute will help to grow and strengthen small to medium size firms with the technical capabilities to support the global pharma industry.
- These developments will in turn lead to increase in overall pharma sector employment including both technical / scientific jobs as well as highly skilled manufacturing associates.
- The improved quality, safety and security of the US drug supply will benefit US patients and support homeland security in times of when international supply lines may be stressed.
- The accelerated development work flow and increased manufacturing efficiency will lead to lower cost of drugs, both innovative and generic, to the US consumer
- The ability of US pharmaceutical manufacturers to insure quality and supply at competitive cost will lead to growth of exports to global markets.
- The availability of innovative manufacturing systems will accelerate the introduction of new types of therapies, which require more complex delivery forms or personalized product dosing regimens.

Manufacturing Platforms

The PMI will advance three manufacturing platforms which address the needs of both small molecule based drugs as well as drug products derived via biological routes.

Platform 1. Continuous manufacturing of existing convenient oral dosage forms
This platform will exploit research accomplishments in converting and operating traditional batch and semi-batch unit equipment as integrated continuous production lines. Both a development scale flexible mini- manufacturing line and a manufacturing scale automated and highly instrumented line will be deployed.

Platform 2: Micro scale manufacturing using fluid processing technology.
This platform exploits new processing concepts such as drop on demand dosage fabrication as well as micro dosing into capsules and vials. This technology allows for small production run manufacturing of dosage, which can be executed in a variety of clinical and institutional settings and would facilitate individualized dosage production.

Platform 3. Downstream Manufacturing of Pharmaceutical Biologics
The focus of this platform is on the conversion of the raw output of the (upstream) biological conversion step into a stable, sterile and high purity product suitable for injection. This platform will implement innovations in lyophilization and fill-finishing, stabilization to prevent formation of aggregates, process sensing and automatic control, process modeling and analytical techniques. The platform will have high relevance not only for innovative drugs but also for vaccines and biosimilars.

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