NIPTTE 2016
From Roadblocks to Roadmap- 2017,
with a 2020 Vision
Ajaz S. Hussain, Ph.D., President NIPTTE
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PREAMBLE

Over a decade ago, the National Institute for Pharmaceutical Technology and Education, Inc. (NIPTE), began a journey to improve awareness of the need and the value of pharmaceutical technology research and education in addressing some of the most significant challenges that repeatedly plague the Nation’s pharmaceutical supply. In May 2006 Senator Luger introduced a draft legislation “Pharmaceutical Technology and Education Enhancement Act” to the US Congress. His introductory remarks described the need and the mission - which NIPTE continues to pursue today (see sidebar).

Dr. Janet Woodcock, Director FDA/CDER reemphasized this mission, at the NIPTE Conference 2016. She suggested that, ideally, academia should be “the third leg of the stool” - to nudge the FDA and the industry to improve their policies and practices.

The FDA’s Process Analytical Technology and the Pharmaceutical Current Good Manufacturing Practices (CGMP) for the 21st Century: A Risk-based Approach initiatives were launched at the beginning of the 21st Century(2). Later these merged with the “Critical Path Initiative” to transform the way FDA-regulated products are developed, evaluated, manufactured, and used (3). Today NIPTE continues to collaborate with FDA to facilitate this transformation.

In 2015 FDA reorganized OPS to the Office of Pharmaceutical Quality (OPQ) and added an emphasis on One Quality Voice (4). In 2017 novel pharmaceutical technologies, the aspirational 21st Century Cures Act (5), and the President-elect Trump’s Administration are juxtaposed to re-shape, perhaps radically so, the Critical Path transformation underway since the beginning of this century.

How will the Nation’s life-science research priorities change? What should be the next steps to optimally integrate 21st Century Quality, Cures and the Voice of Patients? What can/should NIPTE do next? Do better? Do more - be the third leg of the stool? This report, From Roadblocks to Roadmap 2017, with 2020 Vision, reviews and reflects on strategic directions emphasized by NIPTE in 2016. It recommends ways to strengthen the Voice of NIPTE to advocate its mission more persuasively and to facilitate its members apply their full potential in the interest of the Nation.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>NIPTE &amp; FDA/CDER Office of Pharmaceutical Science (OPS) sign a Memorandum of Understanding to work together to progress the FDA initiatives.</td>
</tr>
<tr>
<td>2009</td>
<td>NIPTE awarded FDA contract to develop and conduct continuing education programs for FDA reviewer on state-of-the-art pharmaceutical manufacturing and technology.</td>
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<tr>
<td>2011</td>
<td>Research UO1 grant entitled “Critical Path Manufacturing Sector Research Initiative.”</td>
</tr>
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</table>

S. 2793, A bill to enhance research and education in the areas of pharmaceutical and biotechnology science and engineering, including therapy development and manufacturing, analytical technologies, modeling, and informatics.

Senator LUGAR: Mr. President, I rise today to introduce the Pharmaceutical Technology and Education Enhancement Act. The legislation that I introduce today would improve pharmaceutical and biotechnological development and manufacturing through education and research at our nation’s institutions of higher education.

By expanding pharmaceutical science, technology and engineering research within our universities, this bill aims to expedite the drug manufacturing process thereby producing quality pharmaceuticals at a more affordable cost to consumers.

12/18/2016  NIPTE 2016: From Roadblocks to Roadmap 2017, with a 2020 Vision  2
INTRODUCTION
In 2016 the NIPTE faculty leaders undertook several strategic discussions (see Table 1) that were motivated and informed, among other things, of the reasons FDA/CDER reorganized its pharmaceutical quality oversight function under the new OPQ (see sidebar). From these discussions three areas of strategic emphasis are identified:

1. Center of Excellence for Pharmaceutical Formulations
2. Pharmaceutical Technology Education & Certification
3. Team-based science, as the way to work in NIPTE

TABLE 1: LIST OF SIGNIFICANT NIPTÉ DISCUSSIONS IN 2016

<table>
<thead>
<tr>
<th>Date</th>
<th>Discussions and Key Presentations</th>
</tr>
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<tbody>
<tr>
<td>3/16/2016</td>
<td>Seminar at FDA entitled “NIPTÉ Center of Excellence for Pharmaceutical Formulations” (NIPTÉ speakers included Vadim Gurvich, Ajaz Hussain, Steve Byrn, Ken Morris, Steve Hoag and Raj Suryanarayan)</td>
</tr>
<tr>
<td>5/20/2016</td>
<td>Presentations at the GDUFA Regulatory Science Initiatives Part 15 Public Meeting 2016 under the umbrella topic of “Confidence in Generics: Need for and integrated approach to formulation research and knowledge management.</td>
</tr>
<tr>
<td>8/16/2016 – 10/2016</td>
<td>Round-table discussions* facilitated by Vadim Gurvich &amp; Ajaz Hussain @ University of Iowa*: Integrated Pharmaceutical Development &amp; Regulatory Review: How is NIPTÉ contributing? (*similar discussions held at University of Wisconsin, Purdue, and UT @ Austin)</td>
</tr>
<tr>
<td>8/2/2016</td>
<td>Team-based Science. Faculty leadership meeting and discussion in Silver Springs, MD.</td>
</tr>
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</table>

In parallel to these strategic discussions, significant efforts were devoted to progressing current projects (with FDA and Sun Pharmaceuticals Ltd.) and for developing new proposals (e.g., the National Network for Manufacturing Innovation; NNMI). On 16th December 2016, NIIMBL (The National Institute for Innovation in Manufacturing Biopharmaceuticals) was awarded a $70 million

OPQ: 21st Century Pharmaceutical Quality Initiative
The FDA/CDER OPQ was stood up in 2015 to integrate and streamline - One Quality Voice - quality oversight over product lifecycle across the two functions:

1) regulatory review of drug applications, and
2) inspection of facility compliance with current good manufacturing practices (CGMPs)

OPQ aims to work proactively with the pharmaceutical industry to prevent quality issues from occurring and help mitigate them before quality issues result in drug shortages.

At the launch of OPQ FDA specifically acknowledged that: Significant, technological & policy, progress occurred with the 21st Century Initiative program.

To effectively implement these technological advances in current regulatory procedures and practices the FDA also needed to change and improve.

The launch of OPQ is: 21st Century Initiative 2.0.
cost-shared cooperative agreement with the National Institute of Standards and Technology (NIST). NIPTE and several of its member institutions are among the 70+ collaborators in NIIMBL which seeks to innovate biomanufacturing in America.

Clearly, 2016 was a very significant year for NIPTE. Despite this progress, and, also, perhaps because of it, a question that lingers on—what is (and should be) the role of NIPTE in the Critical Path transformation process. In 2016 the leadership perceived several roadblocks to achieving the proper recognition for NIPTE to contribute to the ongoing transformation process optimally. Their efforts identified three areas of strategic emphasis which will guide the development of the Roadmap 2017.

This report seeks to understand and elaborate on the main roadblocks to NIPTE’s progress. Changes in the macro-environment (sidebar) are considered to inform the development process for the Roadmap 2017. Furthermore, the report shares a perspective on what can/should NIPTE do next? Do better? Do more - be the third leg of the stool?

A framework, 2020 Vision, is a constructed to provide clear sight of opportunities to advance NIPTE’s mission along the 3rd leg of the stool metaphor. Table 2, below gives an overview of this report. Starting with column 1, the questions listed categorize roadblocks discussed. Followed by consideration for Roadmap 2017 and an extend 3-year outlook – the 2020 Vision.

**TABLE 2: OVERVIEW: FROM ROADBLOCKS TO ROADMAP 2017, WITH A 2020 VISION**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Why is NIPTE still crucial to the Nation?</td>
<td><strong>Centers of Excellence (CE)</strong></td>
<td>NIPTE a Certifier of New Prior Knowledge</td>
</tr>
<tr>
<td>How should NIPTE function in 2017 and beyond?</td>
<td>1. Specific population (e.g., pediatric)</td>
<td>a. Certification of Continuing PT Education</td>
</tr>
<tr>
<td></td>
<td>2. Specific quality attribute (e.g., Abuse Deterrence, nano-delivery)</td>
<td>b. Monographs for Quality Target Profile for Generic and Biosimilar</td>
</tr>
<tr>
<td>What should NIPTE contribute in 2017 and beyond?</td>
<td>4. Other centers</td>
<td></td>
</tr>
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</table>

**21ST CENTURY CURES & TRUMP ADMINISTRATION**

Huge bipartisan majorities in Congress supported the 21st Century Cures Act: President Obama signed into law 12/13/2016 (5) The following subtitles are of specific interest to NIPTE:

- A—Patient-Focused Drug Development
- B—Qualification and Use of Drug Development Tools
- Subtitle C—FDA Advancement of Precision Medicine
- Subtitle D—Modern Trial Design and Evidence Development
- J—Domestic Manufacturing and Export Efficiencies
- K—Enhancing Combination Products Review
- P—Improving Scientific Expertise and Outreach at FDA

**New Secretary DHHS & Commissioner of FDA**

Added push to speed up regulatory approvals and reduce regulatory burden

*Revitalize US manufacturing*

PDUFA, BsUFA & GDUFA: OPQ & OGD Priorities 2017
THE 3RD LEG OF THE STOOL: 2020 VISION

Reliability of the Nation’s pharmaceutical supply is critical. Unfortunately, it is often called into question because of recurring drug shortages, recalls, warning letters, import alerts, and other failures (4). Gaps in pharmaceutical technology applications (6) and education (7, 8) are at the root of many of these challenges; attempts at correcting and improving the system often do not get to these underlying causes.

Over the past decade, the rapid rate of globalization exposed several vulnerabilities, and Dr. Woodcock had to issue a call to revitalize pharmaceutical manufacturing in the USA (9). Her request was founded on a recognition of the potential for higher assurance of quality and reliability via technologies for real-time measurements and controls and continuous manufacturing.

Today this call reverberates loudly in the 21st Century Cures Act, in NIIMBL, and is juxtaposed with the priorities of President-elect Donald Trump.

The process of transformation is like 'building a plane in the sky.' Agenda of the FDA User Fee Programs (PDUFA, GDUFA, & BsUFA) for 2018-2022, have been proposed or set (10-12). Technological Progress is only a step in the transformation process. For the paradigm to shift the current heterogeneous practices and set-minds that will need to change. Recognizing some of these challenges, the FDA reorganized its quality oversight function to create the OPQ and added an emphasis on One Quality Voice (4).

[Re-]education and continuing education, in the context of 21st Century Quality, are urgently needed to build expertise and to help current practitioners, who are distributed globally, to recognize the need, the reality and the technological opportunities of the 21st Century to re-set their minds.

The need for One Quality Voice plus the increasing material, professional, organizational and geopolitical complexities, calls for a strong academic voice, metaphorically, the third leg of the stool. On matters related to technological and educational solutions and to improve assurance of pharmaceutical quality the Nation is in need of an organization such as NIPTE (not-for-profit, multi-university, etc.) to serve as the 3rd leg of the stool. If NIPTE chooses to step-up, it should, among other things, contemplate the following responsibilities:

- NIPTE Reports to the Nation: (a) State of Nation’s Pharmaceutical Quality Assurance System, and (b) Recommendation on Pharmaceutical Technology Research & Education Priority

- NIPTE a Certifier of “New Prior Knowledge”: (a) Pharmaceutical Technology Continuing Education & Certification Criteria, and (b) Monographs on Quality Target Profile for Generic and Biosimilar Products to complement compendial & other public standards

NIPTE VISION & MISSION

Our Vision ...to be the recognized world leader in pharmaceutical technology and education to improve human health through excellence in research, education, and collaboration. NIPTE will create a paradigm shift in how medicines are designed, developed and manufactured. NIPTE will be an advocate for scientific advances to optimize the application of pharmaceutical technology to improve human health.

The mission of NIPTE is to improve human health through multi-university collaborative to advance the quality, safety, affordability and speed to market of medicines through interdisciplinary research and education in pharmaceutical technology.

A paradigm shift is a fundamental change in the basic concepts and experimental practices of a scientific discipline (Kuhn).

Pharmaceutical Quality by Design, is a paradigm and a methodology, awaiting a shift in “Good” development, review, manufacturing, quality assurance and inspectional practices!
2016 NIPTE STRATEGIC THEMES

The preposition for in the National Institute for Pharmaceutical Technology & Education was reasoned to describe its goal; facilitating its member universities sustain and strengthen their research and education programs that are critical to National interests. NIPTE, in part via the experience gained by the FDA U01 Research Grant in 2011, has become very proficient in its ability to rapidly respond to FDA’s research needs and to assemble multi-disciplinary teams to meet the demands for Requests for Proposals (RFPs). Building on this capability, in 2016, NIPTE sought to highlight the value of, and to leverage the strength in, its multi-university collaboration for offering solutions for the optimal and the integrated development of pharmaceutical formulations and in their regulatory assessment.

The efforts initiated in 2016 (Table 1 and sidebar on the right) sought to reflect on its abilities to:

- Showcase its capacity to undertake large multi-disciplinary projects,
- Express interest to translate science into policy and to facilitate transformation in current practice,
- Inform FDA about current gaps and educational needs, and recommend research priorities

NIPTE’S CENTER OF EXCELLENCE (CE) IN PHARMACEUTICAL FORMULATIONS

CE is to provide an integrated approach to understanding (complex/critical) drugs and dosage forms, convert accumulated information into a public knowledge base and to translate that to FDA and industry through education and tools. This proposal aimed at highlighting the need to generate fundamental understanding and expertise on formulations, of the many nuances and critical aspects of manufacturing and how processes influence formulations in the context of stability, bioavailability, and potential failure modes. To effectively achieve this goal such a Center would serve as a curator of pharmaceutical technology knowledge and builder of an informatics system.

THE CENTER WOULD SUPPORT FDA

- FDA’s asking the right question – at the right time critically contributes to effective and efficient development of pharmaceutical products
- To ask the right question at the right time, FDA needs portions of development reports available for review by reviewers with the necessary technical expertise

STRATEGIC EFFORTS & THEMES 2016

Center of Excellence for Pharmaceutical Formulations

Confidence in Generics: Need for and integrated approach to formulation research and knowledge management

NIPTE’s recommendations on research priorities in FY 2017 GDUFA Regulatory Science Program (Docket: FDA-2013-N-0402; 16 June 2016)

Gabapentin—Optimizing Design Space Specifications Across Scales with Considerations to Stability

Objective risk assessment via asking the right question at the right time: Knowledge-based decisions for dosage form design/development/control.

Pharmaceutical Technology, Education and Confidence in Assurance of Quality

Interest and Effort to Fill Gaps in Education Need – Industry and FDA.

Team-based Science - NIPTE’s Interest and Efforts to Support Integrated Scientific Development of Pharmaceutical Products.
Until the implementation of ICH Q8 – FDA CMC Review was structured not to review development reports (the old “Art not Science” argument).

Even with ICH Q8 – optimally useful/congruent review of new drug development reports is yet to be achieved across the ICH regions, so the time is right for facilitating this in the U.S.

With the formation of OPQ and the efforts to align new chemical and biotech drugs and generic and biosimilar CMC review process, the question-based review approach holds promise but is in need of significant update and attention to ensure it is efficient and that it facilitates development efficiency;

With the curation of knowledge and developing an NIPTE network of experts could be a way forward; not just in the USA but across the world; and

One of the most valuable components is that this can incentivize fundamental and applied research in the most relevant domains on an unprecedented scale.

PROPOSED BENEFITS OF THE CENTER MODEL

- Develop knowledge and understanding of FDA
- Science-based review assessment of “Pharmaceutical Equivalence.”
- Facilitate evaluation of generic submissions
- Develop standards for formulations and excipients
- Develop standard test methods
- Facilitate approval of pediatric formulations
- Faster post-approval changes
- New innovations
NIPTÉ’S RECOMMENDATIONS ON RESEARCH PRIORITIES FY 2017 GDUFA REGULATORY SCIENCE PROGRAM

An NIPTÉ team sought to highlight research and education needed to address ongoing challenges related quality of the submission (multiple review cycles), need for on-time approval of ‘first generics’ and the FDA’s expressed concern on the vulnerabilities in the global supply. These issues, as illustrated in the figure (right) were described in a recent testimony of Dr. Janet Woodcock to the House Committee on Oversight and Government Reform (13).

SPECIFIC CONTRIBUTIONS & NIPTÉ TEAM

1. Confidence in Generics: Need for an Integrated Approach to Formulation Research and Knowledge Management. Ajaz Hussain
2. Mechanism for an integrated approach to Formulation Research, Knowledge Management, & Knowledge sharing with FDA & Industry. Steve Byrn
3. Integrated approach for evolving standards for formulation design - case example Narrow Therapeutic Index drugs (NTI’s). Ken Morris
4. An integrated approach for evolving standard for analytical characterization - case example excipient variability. Eric Munson

These presentations emphasized, with examples, some of the challenges in generic drug development and review; time crunch, and increasing the complexity of the materials and product attributes, growing the need for extensive analytical characterization and of information integration to assess the weight of evidence. Increasing complexity poses a disproportionally higher risk to maintaining & improving confidence in generic drugs. Protracted and expensive development, multiple review cycles, and delayed launch dates (for reasons beyond IP issues) are at the risk of becoming the norm. Competition, even among generics, is decreasing; consolidation is on the rise and so are generic prices. There is an increased risk of continued challenges to approved complex generics (e.g., via continued analytical characterization post approval) and there are many reasons for significant delays; particularly to the on-time approval of first generics.

NIPTÉ RECOMMENDATION: FY 2017 GDUFA REGULATORY RESEARCH

Confidence in generic drugs is built upon an optimal integration of evidence derived from formulation and process design, analytical characterization and, confidently knowing when in vivo assessment is necessary. In their allocation of FY 2017 funding for GDUFA regulatory science research, the FDA is urged to consider prioritizing efforts towards the development of knowledge bases and standards to guide optimal development and integration of the multifaceted scientific evidence of Therapeutic Equivalence (recommendations were submitted to the FDA Docket: FDA-2013-N-0402).
TEAM-BASED SCIENCE PRACTICE IN NIPTE

Towards the end of 2016 (in October) it increasingly became apparent that NIPTE needed to adopt and promote the practice of team-based science. Eric Munson (Chair, Faculty Committee) led this discussion at a faculty meeting on 2 October, and he presented NIPTE’s perspective on the topic at the annual conference on 4th October. The information below is derived from his presentation.

WHY TEAM-BASED SCIENCE?

NIPTE is an organization that has many, if not most, of the [pharmaceutical technology] content experts in their respective disciplines. Typical faculty members work individually on projects, and often lack perspective or understanding [of the regulatory context]. NIPTE lacks coordinated goals, interdisciplinary interactions; e.g., Pre-formulation, Formulation, and Manufacturing.

<table>
<thead>
<tr>
<th>Synergy</th>
<th>Need to rely upon team-based science to drive advances in the understanding of drug substance and drug product. Educational opportunities to drive consensus knowledge</th>
</tr>
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<tbody>
<tr>
<td>Teamwork</td>
<td>Necessary to solve complex problems, a collection of people with different areas of expertise are needed. Previous example: Gabapentin</td>
</tr>
<tr>
<td>Predictive</td>
<td>Ability to predict quality and performance is essential</td>
</tr>
<tr>
<td>Proactive</td>
<td>The regulatory system is reactive, and impetus to change is harm caused to patients. Cumulative approach to regulations keeps the system in a reactive mode.</td>
</tr>
<tr>
<td>Translational</td>
<td>NIPTE research should be used to propose regulatory policies and guidance</td>
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SHOWCASE TEAM-BASED: GABAPENTIN PROJECT

The project entitled “Gabapentin—Optimizing Design Space Specifications Across Scales with Considerations to Stability” was recognized within NIPTE as exemplary of team-based science and it was showcased at the NIPTE Conference 2016 by Lee Kirsch.

| 14 Peer-reviewed publications; 4+ manuscripts in preparation |
| 7 Doctoral theses; partially or wholly based of project data |
| 10 graduate students and 10 post-doc and research scientists trained |
| 40+ invited presentations; 50+ posters |

The scholarly output of this one project is clearly impressive. It's translational contributions, regulatory recognition and utility – however, remain unconfirmed and unrealized.
CONTINUING EDUCATION AND CERTIFICATION

At the NIPTE Conference 2016, the NIPTE keynote address was entitled “Pharmaceutical Technology, Education and Confidence in Assurance of Quality” by the author to emphasize an urgent need for all to pay attention to pharmaceutical technology education and certification. In summary, the following arguments were presented: pharmaceutical quality decisions are made by multidisciplinary teams, at different times and in various organizations. Knowledge and understanding of the Quality by Design (QbD) paradigm (the mindset; a way of thinking) and methodology (for example as outlined in ICH Q8 Guideline) continues to be derived experientially (weak in epistemology). The challenge of integrated development and review cannot be underestimated - “One Quality Voice” is hard to achieve! Legacy challenges, different ontological assumptions, and weak epistemology curtails knowledge sharing, delays consensus and keeps us trapped in a reactive mode. The risk of irrational decisions is often not adequately accounted. Continued “cut-paste” or “check-the-box” practices are constant reminders that we – the pharmaceutical community - are not achieving an optimal integration or practicing systems thinking. A reactive approach to filling the noted gaps poses a risk of continued erosion in the confidence the public should have in our assurance of pharmaceutical quality. There is an urgent need for a thoughtful, planned approach to filling these gaps – NIPTE can and should take on this challenge!

NOT SCIENTIFIC TO SCIENTIFIC

It should be appreciated that in 1995 when the author joined the FDA, CMC review did not utilize pharmaceutical development reports – primarily because the information contained was not considered “scientific.” In 2005, ICH Q8 guideline outlined a methodology for quality-by-design; which had been and continued to be, the paradigm (plan-do-check-act) for CGMPs. A systems orientation and product life-cycle considerations are necessary. The problems at hand need to be defined carefully and compressively.

LAUNCH OF NIPTE-SUN PHARMA EDUCATION AND CERTIFICATION PROGRAM

This exciting collaboration was initiated in October 2016, and it aims to develop a customized Pharmaceutical Quality by Design Education and Certification program. This program is targeted for staff in multiple functions and at multiple levels. The program is expected to span up to five years. Raj Sury serves as the Chairperson of the NIPTE Curriculum Committee. At the NIPTE Conference 2016 @ FDA Sury presented on “NIPTE’s Interest and Effort to Fill Gaps in Education Need – Industry and FDA.”
2016 OBSERVATIONS AND ASSESSMENT OF IMPACT MADE BY NIPTI

OFFICE OF PHARMACEUTICAL QUALITY: CHALLENGES & FOCUS AREAS

In a review article published in 2016 (14) leaders of OPQ and CDER described their science and research focus in three areas:

- testing and scientific investigation of methods and data that aid drug quality evaluation
- proactive research for the development of scientific tools
- approaches for evaluating the safety, performance, and quality of products

In Table 4 their key challenges and focus areas are summarized. A significant shift can be noted in the list of difficulties described in 2016 (14) from the description in late 2014 to early 2015 when OPQ was introduced (4). This point will be discussed in the following section.

TABLE 4. FDA/CDER/OPQ CHALLENGES AND FOCUS AREAS

<table>
<thead>
<tr>
<th>OPQ Challenges</th>
<th>Focus Areas</th>
</tr>
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<tbody>
<tr>
<td>• Product quality failure, mainly manufacturing issues and facility remediation, account for most drug shortages and product recalls in the United States</td>
<td>• Manufacturing and controls for drugs &amp; biotechnology products</td>
</tr>
<tr>
<td>• Science to policy pressures; biosimilars, precision medicine, combination products, emerging manufacturing technologies, and the use of real-world data</td>
<td>• Drug quality standards</td>
</tr>
<tr>
<td>• Pharmaceutical manufacturing is increasingly globalized, prompting the need for more efficient surveillance systems for monitoring product quality</td>
<td>• Advanced characterization of complex mixtures and biologics</td>
</tr>
<tr>
<td>• Increasing scrutiny and accelerated approval pathways provide a driving force to be even more efficient with limited regulatory resources.</td>
<td>• Physicochemical characterization of complex formulations and dosage forms</td>
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<td></td>
<td>• Post-market product quality and public health issues</td>
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<td></td>
<td>• Immunogenicity and immunology</td>
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<td></td>
<td>• Linking biomarkers and drug attributes to safety and efficacy</td>
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</table>

Many of these focus areas (Table 4) are already aligned with some of the provisions of the 21st Century Cures Act. Clearly, control strategy with the real-time release and continuous manufacturing are a primary area of interest. Furthermore, a growing emphasis on ‘clinical relevance of quality specifications’ in conjunction with modeling and simulation can be expected to have a high priority – particularly in the context of specification setting and to justify a less burdensome approach to post-approval changes. It is important to note that ICH Q 12 guidelines is progressing, and perhaps will be released in late 2017 (15).

This guideline is intended to work with ICH Q8 to Q11 Guidelines and will provide a framework to facilitate the management of post-approval CMC changes in a more predictable and efficient manner across the product lifecycle. Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments. It will allow regulators (assessors and inspectors) to understand better, and have more confidence and trust in a firm’s Pharmaceutical Quality System (PQS) for the management of post-approval CMC changes.
OPQ PERSPECTIVE ON HOW CAN NIPTE ASSIST

Michael Kopcha’s (Director OPQ/CDER/FDA) keynote address at the NIPTE Conference 2016 noted how NIPTE could assist the pharmaceutical community and OPQ.

### How Can NIPTE Assist Pharmaceutical Community?

- Establish fundamental understanding of formulations (e.g., API and excipient properties and release mechanism), processes (e.g., batch unit operations at different scales), and their control strategy (e.g., PAT and analytical methods) to aid establishment of knowledge platform in a public domain
- Train and develop future employees for the pharmaceutical industry and FDA
- Serve as a driving force for innovation: “What is next for pharmaceutical technologies?”
- Help to establish guidelines for emerging pharmaceutical technologies

### How Can NIPTE Assist OPQ?

- Complement CDER’s own laboratory capabilities to address agency priorities through science and research
- Help to address emerging quality issues
- Help to develop a formal risk assessment of various combination of formulations, processes and control strategies for regulatory purposes
- Provide training
OBSERVATIONS ON THE PROPOSED NIPTE CENTER OF EXCELLENCE CONCEPT

1. The perspective shared by OPQ, in the context of future collaboration with NIPTE, was indifferent on the CE proposal. The major intent of the CE proposal, establishing fundamental understanding and knowledge platform in the public domain, was appreciated but under the broader context of pharmaceutical community.

2. Potential translational contributions – guidelines for emerging technologies; are also valued in the wider context of pharmaceutical community.

3. For future collaboration with NIPTE, OPQ’s interest appears to remain unchanged (from the current U01 grant format); i.e., the focus remains on complement FDA labs, help address urgent issues; with one possible exception – help OPQ develop formal risk assessment in the context of the control strategy.

4. Training contributions of NIPTE were clearly recognized, and not shown on the slide (above) is the significant request by the Director of the Office of Generic Drugs (Kathleen Uhl) for NIPTE to consider conducting training for the industry.

GDUFA RESEARCH PRIORITIES FY 2017

On 27 October 2017, FDA’s Office of Generic Drugs (OGD) announced how they plan to prioritize GDUFA Regulatory Science funding for (FY) 2017 (16). Their description of FY 2017 priorities is provided below.

- **Post-market evaluation of generic drugs** includes research into monitoring methods, understanding patient perceptions of generic drug quality and effectiveness, and verifying therapeutic equivalence via patient brand-to-generic switching studies. These investigations provide additional data in therapeutic areas where concern exists about the substitutability of generic drugs and allow FDA to verify that generic drugs are fully interchangeable, safe, and effective in comparison to their reference listed drug (RLD). Ongoing activities include evaluating modified release formulations, identifying the role replicate design studies may add to bioequivalence determinations, and piloting surveillance methodologies for generic drugs within FDA’s Sentinel program.

- **Equivalence of complex drug products** includes research into making generic versions available in all product categories, including complex drugs with unique characteristics. FDA spends an increasing amount of time reviewing and developing a policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs. This scientific research supports the development of guidance and policy that clarifies the Abbreviated New Drug Application (ANDA) pathway for complex products, such as drug-device combinations, transdermal systems, implants and parenteral microspheres, nanomaterials (e.g. liposomes and iron colloids), and products that contain complex mixtures and peptides. Research continues into new guidance for transdermal irritation studies and for human factors studies that will aid in the evaluation of product substitutability and robustness for drug-device combinations.

- **Equivalence of locally-acting products** includes research into new bioequivalence methods and pathways for locally-acting drugs. To date, the lack of efficient bioequivalence pathways for locally acting drug products has limited the availability of generic drugs in this category, which includes inhalation, topical dermatological, nasal, ophthalmic, gastrointestinal, and otic drug products. This research priority includes evaluating in vitro alternatives to clinical endpoint bioequivalence studies. Often these in vitro alternatives are based on microstructure characterization (Q3 equivalence) for products that are qualitatively (Q1) and quantitatively (Q2) similar in formulation, with a research goal of guidance for Q3 bioequivalence approaches. To provide access to generic products for which a Q3 approach is not sufficient, research
continues into BE approaches for non-Q1 and Q2 complex formulations for nasal, inhalation, and dermal products.

- **Therapeutic Equivalence Evaluation and Standards** research supports the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery. FDA continues to prioritize research that supports a pathway for generic versions of abuse-deterrent formulations, improves the evaluation of excipients both for safety and for their impact on BCS class III biowaivers, increases our understanding of solid dispersions of low solubility drugs and supports equivalence of modified release solid oral dosage forms. Many of these goals include research related to improving manufacturing quality through advances in process control, continuous manufacturing, and quality metrics, advancing analytical characterization of the release or abuse deterrent mechanisms and improvement to IVIVC/dissolution methods.

- **Computational and Analytical Tools** impact the other four GDUFA regulatory science priority areas and are essential to modernizing the ANDA review process. Modeling and simulation tools that FDA will investigate include physiologically-based pharmacokinetic or absorption models; pharmacodynamic models or clinical trial simulation; systems biology; and quantitative risk modeling. Research priorities for advanced analytical methods include developing methods that characterize peptides and other complex mixtures and that evaluate particle size, surface chemistry, and gene expression for impurities or immunogenicity. Investment in data warehouse infrastructure is needed to further enable computational tools for research and regulatory review, risk assessment and fraud/outlier detection. Research continues in the use of modeling and simulation tools to address questions of substitutability outside the range of traditional bioequivalence studies such as pediatric and geriatric populations or patients taking proton-pump inhibitors and generalization of statistical methods for evaluating in vitro equivalence.

**OBSERVATIONS: NIPTÉ’S RECOMMENDATIONS & OGD PRIORITZATION FY 2017 GDUFA REGULATORY SCIENCE PROGRAM**

1. Priority description for FY 2017 funding (above) is surprisingly broad; in the previous year, for example, new research priorities were specifically identified.

2. This vast, all-encompassing, description of priorities includes several topics of interest to NIPTÉ and member universities; and these would appear to be congruent with the recommendation submitted by NIPTÉ. However, any such conclusion cannot be derived until the time RFPs are issued; it would then become apparent if NIPTÉ’s recommendations were persuasive or not.

3. Over the years, NIPTÉ has actively participated in the GDUFA part 15 public meetings. A list of presentations by NIPTÉ representatives is listed in Table 5 below. Note that presentations by faculty at NIPTÉ member schools, representing themselves, do not appear in this table.

4. NIPTÉ as an organization participated only once in this program– a project on abuse deterrent formulation.

5. Over the years’ faculty at some NIPTÉ member schools (such as Universities of Michigan, Connecticut, Maryland) have been able to contribute to the GDUFA Regulatory Science program; however, as seen in the figure below, these contributions, in the overall scope of this program, are relatively small and appear to be declining.

6. In the chart below, it seems the funding to non-university entities (e.g., CRO’s) shows an increasing trend.
# Awarded GDUFA Regulatory Research Contracts and Grants

<table>
<thead>
<tr>
<th># AWARDED</th>
<th>$ Millions</th>
<th>NIPTE</th>
<th>University</th>
<th>NIPTE University</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2013</td>
<td>2014</td>
<td>2015</td>
<td>2016</td>
</tr>
</tbody>
</table>

## TABLE 5: NIPTE PRESENTATIONS AT REGULATORY SCIENCE INITIATIVES PART 15 PUBLIC MEETINGS (2014-2016)

<table>
<thead>
<tr>
<th>Meeting date</th>
<th>NIPTE Presenter</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 May 2014</td>
<td>Stephen W. Hoag.</td>
<td>Raw Material and Manufacturing Factors Affecting the Quality of Generic Pharmaceutical Products</td>
</tr>
<tr>
<td>16 May 2014</td>
<td>Michael J. Pikal</td>
<td>The impact of Formulation and Process Variations on the Quality of Freeze Dried Products: How do we identify, control, and characterize critical variations?</td>
</tr>
<tr>
<td>16 May 2014</td>
<td>Daniel T. Smith</td>
<td>Research Opportunities in Evaluating Abuse-Deterrent Opioid Formulations</td>
</tr>
<tr>
<td>5 June 2015</td>
<td>Stephen W. Hoag</td>
<td>Research needs in pharmaceutical excipients: implications of a global supply chain</td>
</tr>
<tr>
<td>5 June 2015</td>
<td>James K. Drennen, III</td>
<td>Quality by Design Training for FDA/OGD Staff</td>
</tr>
<tr>
<td>5 June 2015</td>
<td>Raj Suryanarayanan (Sury)</td>
<td>Advanced Characterization of Complex Dosage Forms to Demonstrate Product Equivalence</td>
</tr>
<tr>
<td>5 June 2015</td>
<td>Eric J. Munson</td>
<td>Advanced Characterization of Complex Dosage Forms to Demonstrate Product Equivalence</td>
</tr>
<tr>
<td>20 May 2016</td>
<td>Ken Morris</td>
<td>QBR as an Organizing Principle for the Pre-Approval Development of Generic Drugs</td>
</tr>
<tr>
<td>20 May 2016</td>
<td>Steve Byrn</td>
<td>Mechanism for an integrated approach to Formulation Research, Knowledge Management, &amp; Knowledge sharing with FDA &amp; Industry</td>
</tr>
<tr>
<td>20 May 2016</td>
<td>Ajaz S. Hussain</td>
<td>Confidence in Generics: Need for an Integrated Approach to Formulation Research &amp; Knowledge Management</td>
</tr>
</tbody>
</table>
ROADBLOCKS TO ROADMAP 2017: A COMMENTARY

Over the past several years NIPTE’s activities have focused on conducting research projects under the FDA U01 research grant (2011). This funding support has been tremendously useful to sustain NIPTE. As an organization, NIPTE has improved its ability to respond to FDA’s research needs rapidly and can quickly assemble multi-disciplinary teams to address the described problem. Today the question why NIPTE remains and increasingly so; both within NIPTE and broadly. Merely sustaining the current state will tend to diminish NIPTE’s potential – which was so compellingly described in May 2006 by Senator Luger (1).

Significant changes at FDA and in the macro-environment necessitates NIPTE to adopt a proactive stance on its stated mission and vision (see the sidebar on page 5). The strategic efforts in 2016 sought to build on the established foundation. These efforts sought to understand how to create the capacity needed to identify, describe and prioritize problems that should be addressed to make drug product development and regulatory approval processes more efficient (e.g., on-time First Generic) and effective (e.g., reducing the rate of failures that erode publics’ confidence). These initial steps were intended to move NIPTE on a path (to be described in the Roadmap 2017) towards a more credible and persuasive advocacy of NIPTEs mission.

TRANSLATIONAL NEEDS, ONE QUALITY VOICE & VOICE OF NIPTE

It has been noted that drug shortages, recalls, warning letters, import alerts, and other related challenges reoccur frequently. Some, not all, of these difficulties, can be addressed via the technological progress in PAT based real-time measurement and controls and continuous manufacturing. Today these technologies are on the verge of a Tipping Point – i.e., at “the moment of critical mass, the threshold.” At FDA, there is a sense of urgency, to push forward these solutions. To appreciate this need for urgency, consider the public stance taken by Dr. Woodcock;

In April 2013 - Nobody Can Really Tell Me If FDA Inspections Are Effective (17) and a few months later in December 2013 to the US Congress - These new ways of making drugs could, with the proper strategies, revitalize pharmaceutical manufacturing in the United States (9).

Now consider, how the FDA description of challenges evolved from – at the launch of the OPQ late 2014 and early 2015 (4) to the description in 2016 (14). See Table 6, a significant difference.

TABLE 6. DESCRIPTION OF THE PRODUCT QUALITY CHALLENGE –THEN AND NOW

<table>
<thead>
<tr>
<th>At the launch of the OPQ (4)</th>
<th>Currently in 2016 (14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product recall and defect reporting data demonstrate unacceptably high occurrences of problems attributed to inherent defects in product and process design; these data further indicate failures in the implementation of manufacturing process scale-up as well as routine production.</td>
<td>Product quality failure, mainly manufacturing issues and facility remediation, account for most drug shortages and product recalls in the United States</td>
</tr>
<tr>
<td>There have been alarming shortages of critical drugs over the past few years. Many of these shortages were caused by the use of outdated equipment, reliance on aging facilities operating at maximum production capacity, and lack of effective quality management systems.</td>
<td></td>
</tr>
</tbody>
</table>
Why this shift; from unacceptably high occurrences of problems attributed to inherent defects in product and process design to Product quality failure, mainly manufacturing issues and facility remediation? FDA seeks to make decisions on scientific evidence. Since 2014 a significant amount of funding was directed to testing of drug products from companies under warning letters and import alerts and other products (18). Some results of these studies have been published other have not yet been shared publicly. It would be prudent to consider that these efforts informed the shift in the description of the challenges in Table 6. Clearly, recalls due to design issues such as the case of extended release methylphenidate products have been acknowledged and steps take to correct these (19); furthermore, prevention of such cases is likely to have been embedded in changes in the integrated review process established in the OPQ. In this context, from the FDA’s perspective, the NIPT proposal on CE may have been too broad and focused on (long-term) solutions that are important but urgent.

Returning to the sense of urgency discussion above – the priority of FDA is evident in its research funding: to push PAT based real-time measurement and controls and continuous manufacturing over the Tipping Point. These efforts are expected to get a boost with the 21st Century Cures Act and, perhaps, with the juxtaposition with President-elect Trump’s stated agenda. It is important here for NIPT to note that, unlike the relatively limited scope of FDA’s U01 Research Grant to NIPT (2011), current research grants - particularly those for continuous manufacturing, have a built-in translational requirement. For example to propose “regulations that would govern the introduction and expansion...” (See: insert on the right). This then poses the question:

- Could the omission of a translational requirement in the 2011 U01 grant, inadvertently, handicapped NIPT?

- If so, is this disadvantage also an additional reason why some faculty in member schools prefer to engage with FDA outside of NIPT?

It is proposed that NIPT, as an organization, is in need to re-establish its Voice. The Voice of NIPT is the Voice of Faculty who choose to engage in NIPT, as it was intended to be; the preposition “for” in the National Institute for Pharmaceutical Technology & Education is by design. By this virtue, NIPT defines and celebrates success – as whenever pharmaceutical science, engineering, and technological contributions, by any organization, are translated into policies and practices to improve public health objectives. A reminder of this virtue was published in the first NIPT Newsletter (June 2016):

**You are NIPT and NIPT is You:** It is expected that individual faculty and those working via NIPT may participate in the same conferences under different banners or may compete for research funding. Just remember when you are not carrying the NIPT banner, NIPT is still there to support You. NIPT celebrates the success of Pharmaceutical Technology & Education; within or without NIPT!
NEED FOR PROACTIVE PRACTICE OF TEAM-BASED SCIENCE

Clearly, when presented with a problem, challenge, or an RFP, as in the Gabapentin project, NIPTE can practice *team-based science*. Going forward NIPTE will need to emphasize a proactive practice of *team-based science* to more confidently achieve its *translational objectives* (as in Table 3). This specific need was more broadly recognized within the NIPTE leadership in 2016. How to operationalize such a practice should be elaborated in the Roadmap 2017 with the objective of placing NIPTE on a firmer footing. To do so, NIPTE should consider:

- *What would constitute a proactive practice of team-based science in NIPTE? How should it be operationalized to strengthen the "Voice of NIPTE specifically"?*
- *Given the what and how (above); would such a practice established in 2015 had made the “Voice of NIPTE” more persuasive when in 2016 when it sought to emphasize the need to prioritize and integrated approach to product development, at the CE Seminar at FDA and the topic covered at GDUFA Regulatory Research Public Meeting?*
- *What steps should NIPTE take next (Roadmap 2017-)?*

The substantial literature on *Science of Team Science* and recommendation on the topic by the Nationa Institutes of Health; particular the *Team Science Toolkit* offered by the National Cancer Institute (20) should inform a serious attempt to progress this strategic theme. In doing so, NIPTE and member institutions should consider and account for factors that influence the effectiveness of *Team Science*. The NCI Toolkit suggests: (a) Funding trends; (b) Institutional infrastructure and resources for communication and data sharing; (c) Organizational policies—such as promotion and tenure policies—that impact team-based endeavors; (d) Team processes, including the existence of agreements related to proprietary rights to data and discovery, as well as mechanisms for feedback and reflection; and, (d) Interpersonal dynamics among team members.

NIPTÉ CENTERS OF EXCELLENCE

Operationalizing the concept of NIPTE Centers in 2017 in collaboration with FDA and industry is highly recommended. This strategic theme can provide a basis to create a platform to engage, recognize, reward and motivate individual faculty leaders and faculty teams and to strengthen the *Voice of NIPTE*. Initially, these Center could serve as “think-tanks” to articulate and champion *translational objectives* in the broader context of public health. These ‘think tanks’ would need to be supportive of other efforts (e.g., such as in PQRI or professional associations such as AAPS, ISPE, and PDA) and decidedly different - on academic rigor for defining the problems and in outlining solutions; the NIPTE signature.

Several CEs should be envisioned; for example, Pediatric Formulations, Nano-Formulation, Abuse-deterrent Formulations, Lyophilization, Formulation Design for Continuous Manufacturing, Analytical Characterization & Weight of Evidence, Material Science, New Prior Knowledge and Risk Assessment, Pharmaceutical Knowledge Management, etc. The LyoHUB consortium progressed by several member institutions, outside NIPTE but in collaboration with it, could and perhaps can still be such a CE.

The 21st Century Cures Act is expected to open several new opportunities; some of these possibilities, particularly the subtitle *J—Domestic Manufacturing and Export Efficiencies*, can be supposed to get juxtaposed with President-elect Trump administrations’ intent on reducing regulatory burden and to increase investment in America. The timing of this juxtaposition seems to be coinciding with the expected releases of ICH Q12. Given the
FDA’s surveillance testing efforts starting in 2014, discussed in the context of Table 6 above, all the directional vectors are pointing in the same direction and can be expected to provide the necessary impetus, and help to improve recognition of the need, the urgency and the opportunity to reduce the regulatory reporting burden for post-approval changes; this should be a significant area of focus at NIPTE.

NIPTÉ CERTIFICATION: CONTINUING EDUCATION AND NEW PRIOR KNOWLEDGE

CONTINUING EDUCATION

Perhaps the most underappreciated contribution of NIPTE, this far, had been its educational and certification potential and offerings. This “bind-spot” started to fade starting in 2014. Today request from several FDA leaders has emphasized the need for NIPTE to offer educational programs. Discussions have been initiated with US FDA on developing a joint educational program for the industry. A collaborative education and certification project with Sun Pharma were launched in October 2016. Expressions of interest for similar educational programs have been received from other companies.

Here it will be useful to review in more detail why in 2015 FDA began emphasizing One Quality Voice to progress its Pharmaceutical Quality for the 21st Initiative that was launched a decade ago. This discussion builds on the public stance taken by Dr. Woodcock (above). The following quotes from an FDA paper describe the current state (4):

- Current regulatory review and inspection practices tend to treat all products equally, in some cases without considering specific risks to the consumer or individual product failure modes.

- A disproportionate amount of regulatory attention is devoted to low-risk products and issues, diverting resources needed for the assessment of high-risk products.

- Inspection is not well-connected to knowledge gained from product review. Inspections often cannot cover all products and processes, so they rely on a limited subset of representative products and processes, often without reference to the specifics of the approved application.

- Likewise, product-review is often conducted based on premarketing data from “exhibit” or “clinical batches”; there may be a significant disconnect between these data and the conditions under which the material is manufactured during commercial production.

If within the FDA, in 2016, quality risk assessment can be as unfocused as described above; imagine the challenge across the global supply chain! To say the least, this is a significant gap. Although so recognized more than a decade ago (7), only now it being appreciated more broadly (8). Education is an important opportunity for notable NIPTÉ contribution. The OPQ’s suggestion that NIPTÉ should assist in formalizing risk-assessment should be a major part of the training programs.
Risk-assessment must be based on scientific evidence. To a large extent currently available information and knowledge of pharmaceutical formulation and manufacturing processes is empirical (i.e., without sufficient theoretical basis) and derived experientially (i.e., can be highly variable in its epistemological status). Such knowledge is often not predictive, or generalizable, or objective. The strategic theme “NIPTE Education & Certification” is essential and it should be progressed thoughtfully with an emphasis on defining objective criteria for standardized certification that applies over the lifecycle of pharmaceuticals and covers relevant development, technology transfer, validation and continued process verification processes. There is a critical concept for consideration here – i.e., new prior knowledge which is discussed below. The effectiveness of these programs would need to consider “meeting FDA requirements” – but with an overlay of academic and operational rigor; that which should become the NIPTE signature. Scale-up considerations for the education program and mechanisms for NIPTE Certification in the global supply chain context should be considered. A CE for Continuing Education and Certification may be needed to bring the focus and attention necessary for this vital area of emphasis.

NEW PRIOR KNOWLEDGE

The term new prior knowledge is used here partly in an aspirational context to recognize the extensive research on quality by design, design space and Bayesian methodologies already funded by FDA and conducted by NIPTE member institutions (e.g., the Gabapentin project discussed previously). Aspirational - because the translational opportunities of some of the developed concepts and methodologies remain, to a large extent, unrealized. The qualifier “new” refers to efforts by NIPTE that can judiciously be expended (such to establish mechanism basis, application of modeling and simulation, and or additional experimentation) to improve confidence in prior knowledge for re-use and regulatory decisions.

The objective of new prior knowledge is to improve efficiency and reduce the cost of drug product development, improve clinical relevance of quality specifications, provide confidence in quality risk assessment, support innovation, and continual improvement, and ensure appropriate approval of ‘First Generics” which is a public health need. It should be applicable for New (e.g., support post-approval changes; conventional to continuous manufacturing), Generic and Biotech products. The concept of NIPTE Certification (of the prior knowledge) is conceived as the built-in peer review, challenge and verification that a multi-university collaboration can muster as part of the translational (research to policy to practice) process. In the context of 2020 Vision – this can include NIPTE Monographs that supplement Compendial monographs. The following example is developed to illustrate what new prior knowledge could mean for a generic nasal spray formulation development and approval.

The accompanying figure was constructed using FDA and USP web images to illustrate and demarcate public (e.g., USP monograph and FDA review information available under the Freedom of Information Act) and proprietary information (including patents and exclusivities).
The case example is a 'First Generic' approval of Mometasone Furoate Nasal Spray on 3/22/2016. The information for developing the case example is purposefully limited only to the information shared by FDA (consistent with 21CFR10.85(k)) in their publication entitled "FDA Embraces Emerging Technology for Bioequivalence Evaluation of Locally Acting Nasal Sprays" (21). It is also noted here – for disclosure purposes – that the author served in an advisory capacity, not related to his NIPTE responsibilities, to the sponsor of this product and participated during a formal FDA Scientific Dispute Resolution process. Important facts about this case:

- ANDA was submitted in December 2008 and approved in March 2016; about 8 years in review.
- The generic applicant used a different polymorph so as not to infringe on the RLD patent (additional note from published media sources - in June 2013 a Federal Circuit Court affirmed the dismissed claims that the generic applicant had infringed on the RLD patents).
- The application history included a refuse-to-receive determination, a scientific dispute resolution, and a significant number of amendments.
- In September 2015 FDA published its draft guidance for establishing Therapeutic Equivalence and adopted a weight of evidence approach: (a) Similarities in device and formulation, (b) Equivalent in vitro performance, (c) Equivalent PK studies, and (d) Equivalent local delivery through pharmacodynamic (PD) or clinical studies.
- During the review of the ANDA, it was communicated that "the clinical endpoint BE study was unacceptable to FDA because it used API manufactured from a site that was not intended to produce the commercial batch. The two API batches showed some degree of difference regarding their particle size distribution."
- Note that the conclusion from the already conducted clinical endpoint BE study was that the test and reference products were equivalent; although particle size differences were found in vitro and the pharmacokinetic study. Subsequently, these differences were minimized, and in vitro and PK equivalence was re-established. The OGD's insistence of requiring the sponsor to repeat the clinical study was disputed.
- The dispute was settled and the evidence derived from in vitro data on particle size and shape via the Morphologically-Directed Raman Spectroscopy was accepted for quality risk assessment (stability of particle size and shape across appropriate environment conditions in which the product may be used and stored).
- In its publication, the FDA stated that - Successful use of this technology sets a precedent to accept an in vitro approach instead of a clinical endpoint BE study. It opens the possibility to change the FDA's historical paradigm for the BE evaluation of locally acting nasal suspension products (the weight-of-evidence approach).
- The new prior knowledge would build on this prior knowledge to facilitate approval of other generic nasal spray and similar products where physical attributes (e.g., size and shape of particles) are critical to facilitate single cycle development and FDA approval.

Other examples of "new prior knowledge" can include -

- Quality Target product Profile for generics and biosimilars derived following extensive characterization of RLD samples to obtain information about the Critical to Quality Attributes (CQAs), acceptable ranges, and stability consideration based on potential failure modes.
- Description of analytical methodology for in vitro characterization of the reference products; justification of analytical methods used and their validation, and methodology for integrated equivalence assessment. Note that heterogeneity in the interpretation of equivalence, in the context of the weight of evidence, needs to be reduced. Especially for building consensus on conditions when in vivo studies should not be required.
• FDA can potentially adopt the information package (above) as its guidance, or such information may be offered as an NIPTE Monograph for industry to use and reduce their development time and cost and achieve FDA approval in one single review cycle

• Considering the previous discussion on “the 3rd leg of the stool” concept; the NIPTE Monograph can be analogous to, and supplement, the USP Monographs; particularly for a complex product that increasingly requires extensive analytical characterization of material functionality and product performance attributes that are not in the scope of traditional Compendial monographs.

Note: Previously recognized roadblocks to generation of new prior knowledge

A large proportion of pharmaceutical development and manufacturing information content in the public domain is in the context of approval decisions that are predominantly based on clinical trials. The relationship between quality attributes and clinical safety and efficacy are often not clearly evident (quality – to -clinical gap). Moreover, as discussed, these data are often empirical (i.e., weak theoretical basis) and derived experientially (weak epistemology). Application of new analytical methods to existing products is discouraged in practice – what if we find something new- is a major concern which is a significant roadblock to continual learning and improvement in the regulated sector. The FDA’s PAT Guidance (22) specifically attempted to address this concern:

When using new measurement tools, such as on- or in-line process analyzers, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate these data to determine how or if such trends affect quality and implementation of PAT tools. FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool. FDA’s routine inspection of a firm’s manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods). Any FDA decision to inspect research data would be based on exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.3004 Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner.

Integrated Application of NIPTE Education & New Prior Knowledge Certification

The real-time controls and continuous manufacturing ‘tipping point’ can ideally be supported via an integrated NIPTE education & new prior knowledge certification program targeted to support the combined regulatory intent in several guidance documents (PAT, FDA’s Process Validation 2011, ICH Q8 -11 and the anticipated Q 12). NIPTE pharmaceutical engineering members have made outstanding contributions already – and NIPTE Board and faculty leaders visited Rutgers in 2016 to appreciate these contributions (see picture insert). Today the higher level of quality assurance potential of real-time controls is formally being recognized by FDA and other regulators. An integrated NIPTE certification can conceptually be positioned as a quantifiable risk-mitigation contribution in the (expected) FDA calculus (of facility risk classification and in reducing burden for a post-approval change). Furthermore, in the context of the 3rd leg of the stool; the concern related to Narrow Therapeutic Index drugs (Submitted to Docket: FDA-2013-N-0402; (23)) can, and preferably should, be recast as an NIPTE advocacy position to help guide and prioritize regulatory efforts and research funding under the subtitle J of the 21st Century Cures Act.
CLOSING REMARKS

Today NIPTE’s mission can not be clearer and its resolve stronger. The strategic themes identified in 2016 are very relevant to address several roadblocks in the progress of NIPTE. Building on these topics the steps we take next can and should put NIPTE on a path that would:

- Allow NIPTE to more effectively contribute independently and collaboratively in the various efforts being undertaken (e.g., NIIMBL, other FDA supported centers, etc.) for building a comprehensive pharmaceutical technology research and education based solutions to address the recurring challenges in the assurance of pharmaceutical quality. Currently, these challenges create system vulnerable and leave the Nation wanting for constant availability and affordability of high-quality medicines.

- Facilitate communication and engagement, the Voice of NIPTE, necessary to convince the US FDA, industry, the US Congress, the US Administration and the American public of the need and value of the contributions NIPTE can provide and explain why these should be an integral part of the Nation’s pharmaceutical quality management system.

The journey ahead will not be easy. With a commitment first to Team Science, the core leadership team can bring their learnings from the strategic discussions (Center of Excellence for Pharmaceutical Formulation and Education and Certification programs) in 2016 to create a Roadmap 2017- that will let confidently begin this new journey.

Development of the Roadmap 2017 is envisioned to occur in phases. This report is written to occupy position the purple arrow; i.e., between the phase How NIPTE adds Value (2016) and Develop Roadmap (January -February 2017).

Table 7 below, provides an overall summary of the discussion in this report. In it, the macro-environmental directional vectors and aligning themes, the stated FDA priorities and the NIPTE’s strategic interests are juxtaposed. This arrangement should make easier to visualize the possible interrelationships among these topics and assist in the development of Roadmap 2017. NIPTE’s proposed solutions and prioritization for public research funding can then be compared with the current focus areas and priorities at FDA. The macro-environment factors are useful. The roadmap, however, should primarily be informed of the challenges faced by FDA and industry in realizing the objective of the FDA’s Pharmaceutical Quality for the 21st Initiative 2.0. In this context, reasons why FDA made significant organizational changes and added an emphasis One Quality Voice, are essential to understanding (4, 14).

NIPTE’s mission to support its faculty conducting basic research is always an important consideration. Although this was not discussed in the report, the column under the 2020 Vision heading maintains this focus. An opportunity to establish NIH Center Grant (e.g., Pediatric Formulations) is also recognized. The Roadmap 2017 should also address these possibilities.
When necessary NIPTE should consider appropriate ‘nudges’ to help overcome inertia within the system. This and success of current projects can allow NIPTE move forward, with 2020 Vision, to play a more important role – the third leg of the stool.
The perspective gained as an observer of the pharmaceutical sector from outside of it, i.e., while working on tobacco harm reduction in Switzerland 2009-2012; and more recently as an advisor to several companies, point to the critical importance of the need to give attention to continued adult human development or maturity (in cognitive, intrapersonal and interpersonal dimensions). How this development and maturity translates to the design of pharmaceutical products and in the assurance of pharmaceutical quality is not adequately or specifically considered in the current Human Resource Systems. NIPTE Certification should consider addressing this gap. For example, the regulatory CGMP requirements at 21 CFR 211.25 on education, training, and experience today have very limited regulatory utility; they are not on a solid theoretical foundation and nor can they be expected to have a meaningful practice utility in its current state (24).

Systems thinking is an essential element of a systems approach to quality assurance; it requires a level of maturity - the 4th level – the ‘Self-authored mind’ in the context of Constructive Development Theory of adult human development progressed by Prof. Robert Kegan and others. For adult human development to progress what we know is important but how we know what we know (i.e., epistemology) is essential. Unfortunately, in the current state, a majority of the practitioners are dependent (check-the-box) on FDA’s guidance, Form 483 observations and Warning Letters as the source of learning and decision-making; this tendency fits on the 3rd level – the ‘Socialized Mind’ and points to the set mind change needed for the transformation we seek (25).

NIPTE is well positioned to help change this state – but to do so, it will need to practice Team Science and aspire and work towards becoming a credible 3rd leg of the stool. To get-it-right in the 21st Century, let’s remember Einstein’s challenge that we will never solve the problems tomorrow with the same order of consciousness we are using to create the problems of today! When we chose to take off our blindfolds, and we commit to recognizing that pharmaceutical quality is like an elephant in the dark; Rumi’s centuries old strategy can still work for us - If each of us held a candle there, and if we went in together, we could see it. Ultimately, this is what Team Science is all about.

Time present and time past
Are both perhaps present in time future,
And time future contained in time past.
If all time is eternally present
All time is unredeemable.
What might have been is an abstraction
Remaining a perpetual possibility
Only in a world of speculation.
What might have been and what has been
Point to one end, which is always present.
Footfalls echo in the memory
Down the passage which we did not take
Towards the door we never opened
Into the rose-garden. My words echo
Thus, in your mind.
But to what purpose
Disturbing the dust on a bowl of rose-leaves
I do not know.

FOUR QUARTETS: BURNT NORTON by T.S. Eliot
REFERENCES


Additional notes:

- Presentation at the NIPTE Conference 2016 @ FDA are posted at http://nipte.org/october-2016-conference
- Photo credit: Sun Academy – 2nd graduation ceremony and launch of the collaboration with NIPTE
- All internet links provided above were again accessed on 18 December 2016.