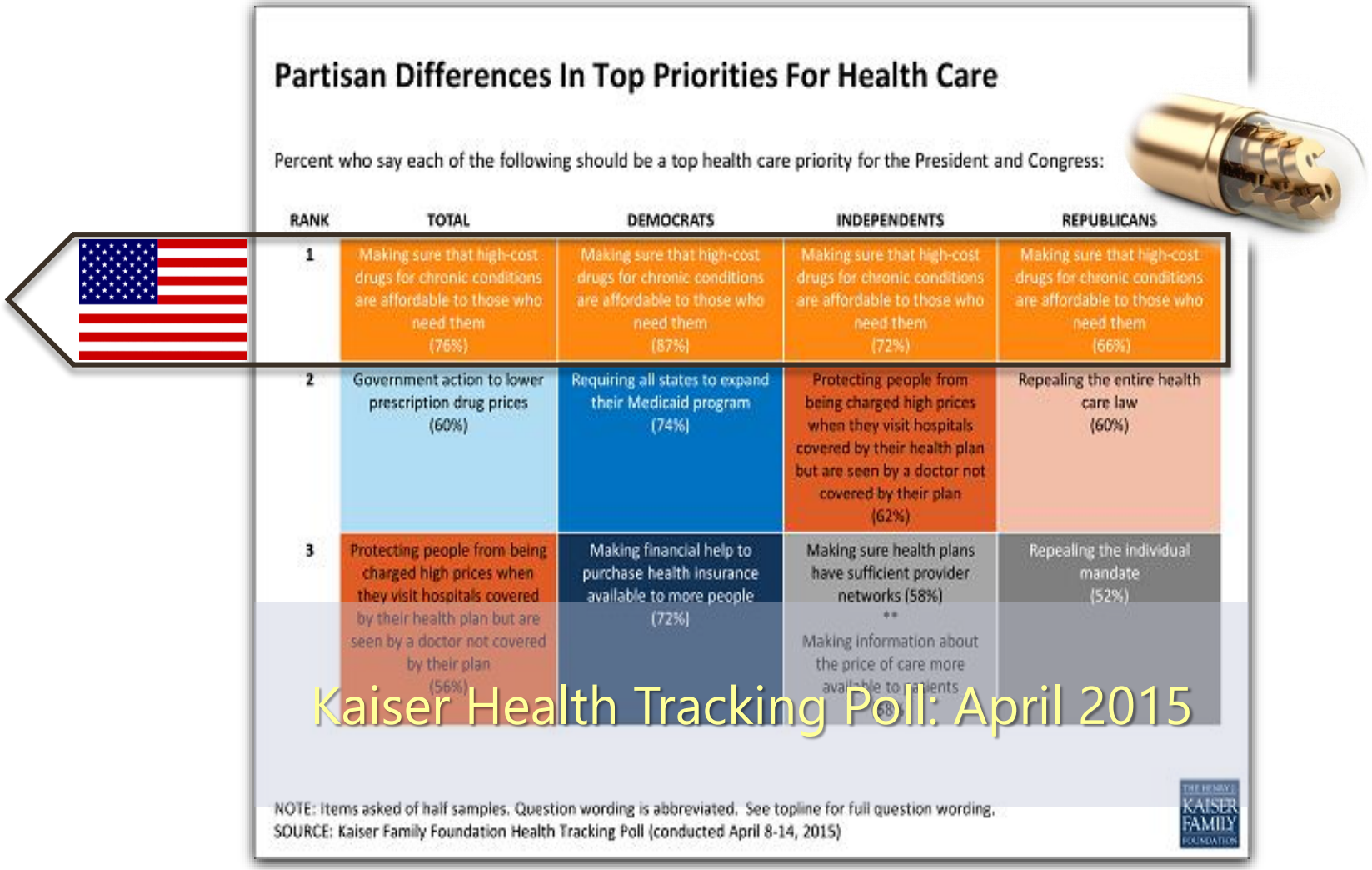
Looking Forward: Beyond 2015

NIPTE Research Conference: Pharmaceutical Critical Path Manufacturing - 2015

Ajaz S. Hussain, Ph.D.
Executive Director

NIPTE The National Institute for Pharmaceutical Technology and Education
Improving quality and lowering costs of pharmaceuticals
Improving quality • Lowering cost • Enhancing confidence

Nation Needs



Partisan Differences In Top Priorities For Health Care

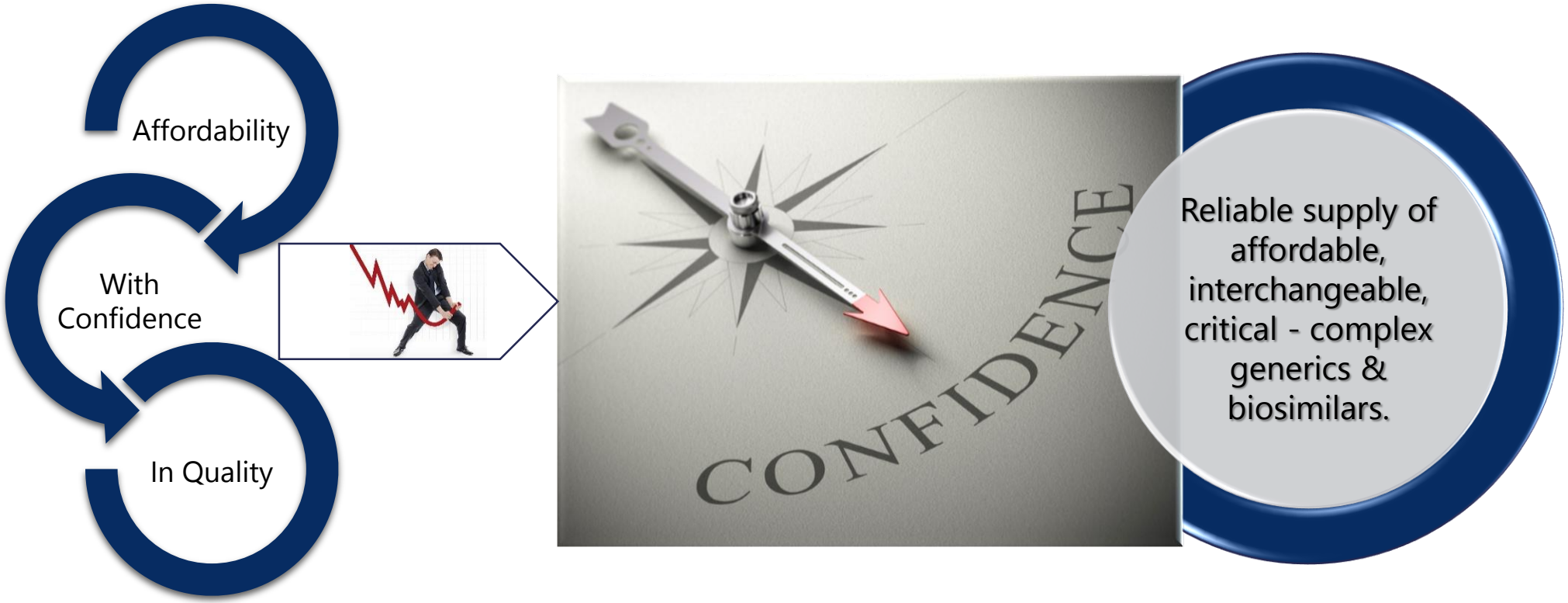
Percent who say each of the following should be a top health care priority for the President and Congress:

RANK	TOTAL	DEMOCRATS	INDEPENDENTS	REPUBLICANS
1	Making sure that high-cost drugs for chronic conditions are affordable to those who need them (76%)	Making sure that high-cost drugs for chronic conditions are affordable to those who need them (87%)	Making sure that high-cost drugs for chronic conditions are affordable to those who need them (72%)	Making sure that high-cost drugs for chronic conditions are affordable to those who need them (66%)
2	Government action to lower prescription drug prices (60%)	Requiring all states to expand their Medicaid program (74%)	Protecting people from being charged high prices when they visit hospitals covered by their health plan but are seen by a doctor not covered by their plan (62%)	Repealing the entire health care law (60%)
3	Protecting people from being charged high prices when they visit hospitals covered by their health plan but are seen by a doctor not covered by their plan (56%)	Making financial help to purchase health insurance available to more people (72%)	Making sure health plans have sufficient provider networks (58%) ** Making information about the price of care more available to patients (68%)	Repealing the individual mandate (52%)

Kaiser Health Tracking Poll: April 2015

NOTE: Items asked of half samples. Question wording is abbreviated. See topline for full question wording.
SOURCE: Kaiser Family Foundation Health Tracking Poll (conducted April 8-14, 2015)

Nation Needs



Nation Needs

Historically, we react

Crisis & errors

Errors/failure are our drivers: Laws and regulations to change behavior

Elixir of Sulfanilamide

Thalidomide

Generic Drug Scandal

Heparin Disaster

Deadly Meningitis Outbreak

1937

FD&C Act

1962

Kefauver-Harris

1989

2007

1984 Drug Price Competition and Patent Term Restoration Act

FDASIA

2012

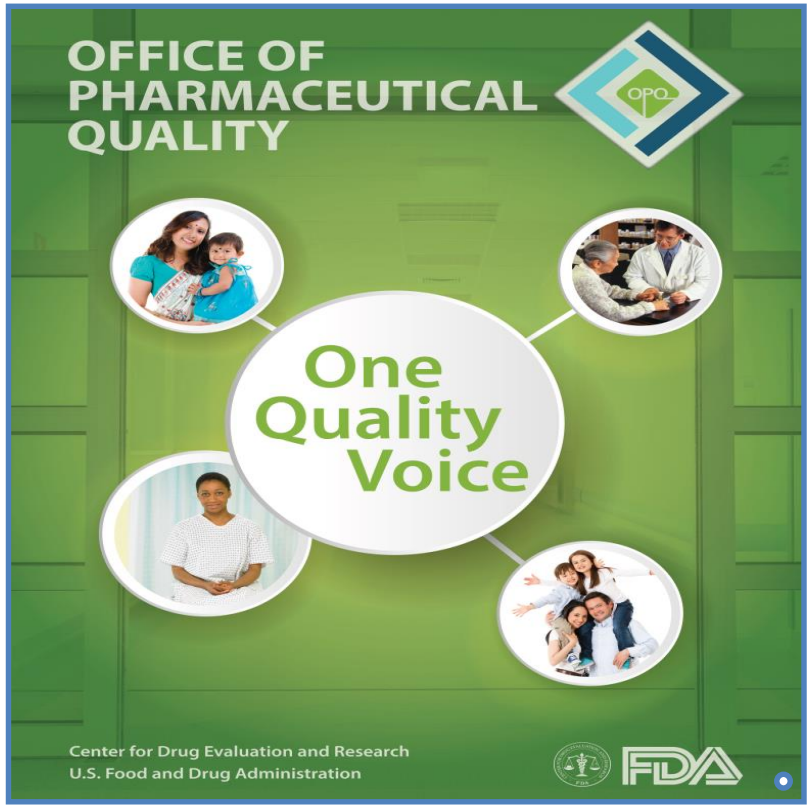
Incresing bars to signify incresing requirments.

……

CAPA Vs. Continual Improvement!

A partial, historical, 'snap-shot' of the US FD&C Act

FDA moves towards



- CDER Office of Pharmaceutical Quality

OPQ = "Integrated"

Today FDA will share with NIPTE their aspirations for the Office of Pharmaceutical Quality

- Assuring that All Human Drugs Meet the Same Quality Standards to Safeguard Clinical Performance
- Enhancing Science- and Risk-based Regulatory Approaches
- Transforming Product Quality Oversight from a Qualitative to a Quantitative and Expertise-based Assessment
- Product Quality Informatics
- Quality Metrics
- Question-based Review
- New Inspection Protocol
- Providing Seamless Integration of Review, Inspection, Surveillance, Policy, and Research
- Team-based Integrated Quality Assessment (IQA)
- Program Alignment across FDA
- Encouraging Development and Adoption of Emerging Technology
- Quality Information in BLAs/NDAs/ANDAs – how does it link to patients?

Quantifiable statistical confidence

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

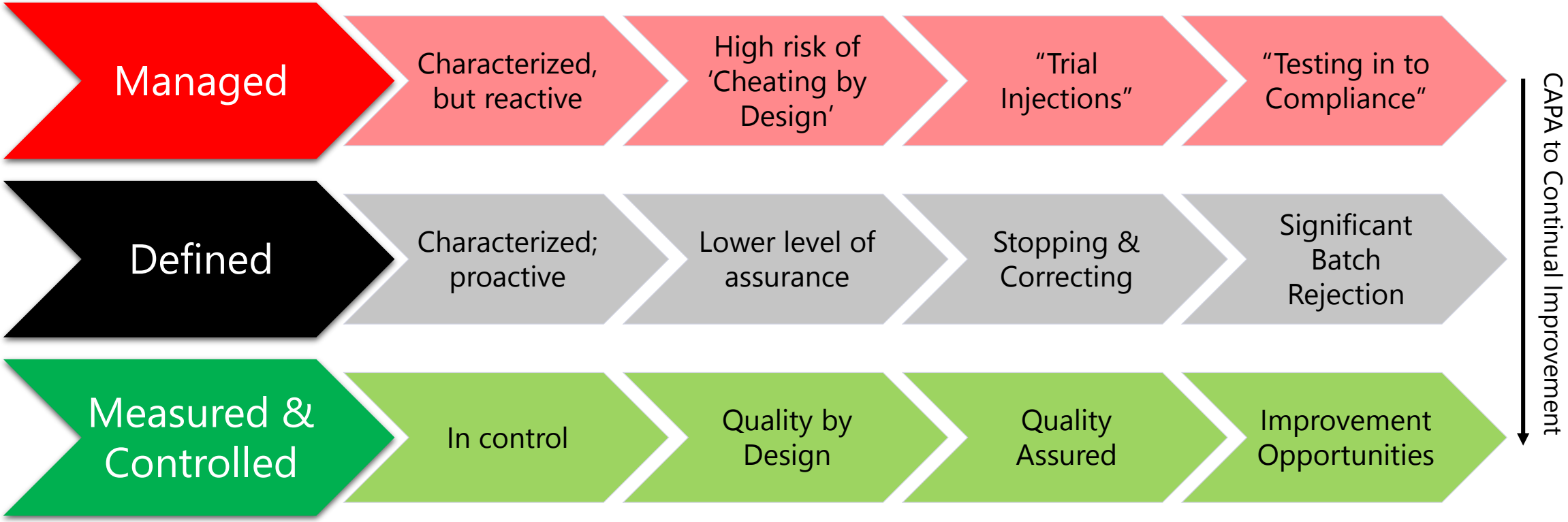
USP 33–NF 28 Reissue General Notices

- At times, compendial standards take on the character of statistical procedures, with multiple units involved and perhaps a sequential procedural design to allow the user to determine that the tested article meets or does not meet the standard. **The similarity to statistical procedures may seem to suggest an intent to make inference to some larger group of units, but in all cases, statements about whether the compendial standard is met apply only to the units tested.**
- Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations, as well as the necessity and appropriate frequency of batch testing, are neither specified nor proscribed by the compendia. First-party (manufacturer), second-party (buyer), or third-party (regulator) compliance testing may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies

GEMcNally, FDA, May 6, 2011 36

- **Using Process Capability To Ensure Pharmaceutical Product Quality**
  - Lawrence X. Yu, Daniel Y. Peng, Robert Lionberger, Alex Viehmann and Karthik Iyer
  - Pharmaceutical Engineering March/April 2015
  - *This article introduces the definition and calculation of process capability, illustrates their use in the pharmaceutical industry, and describes the relationship of process capability with production batch failure rate. The use of process capability in product development, process scale up and qualification, and commercial production is also described.*

Improvement when a process is 'measured & controlled'



Current practices & Continual Improvement

From CAPA to Continual Improvement

Continual vs. continuous

- *Continual*: happening frequently, with intervals between
- *Continuous:* without interruption

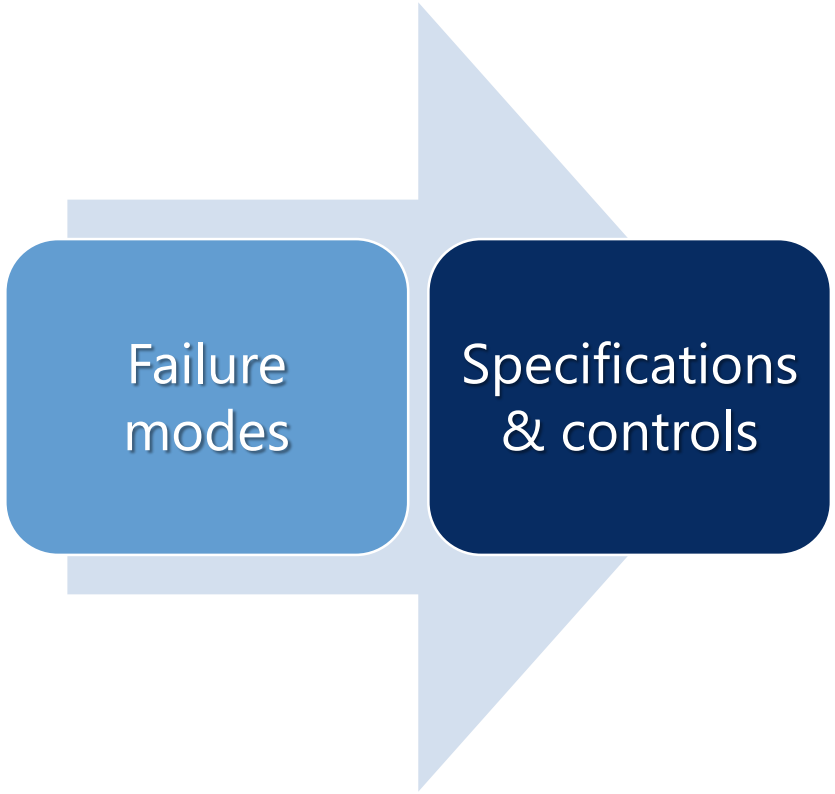
Verification

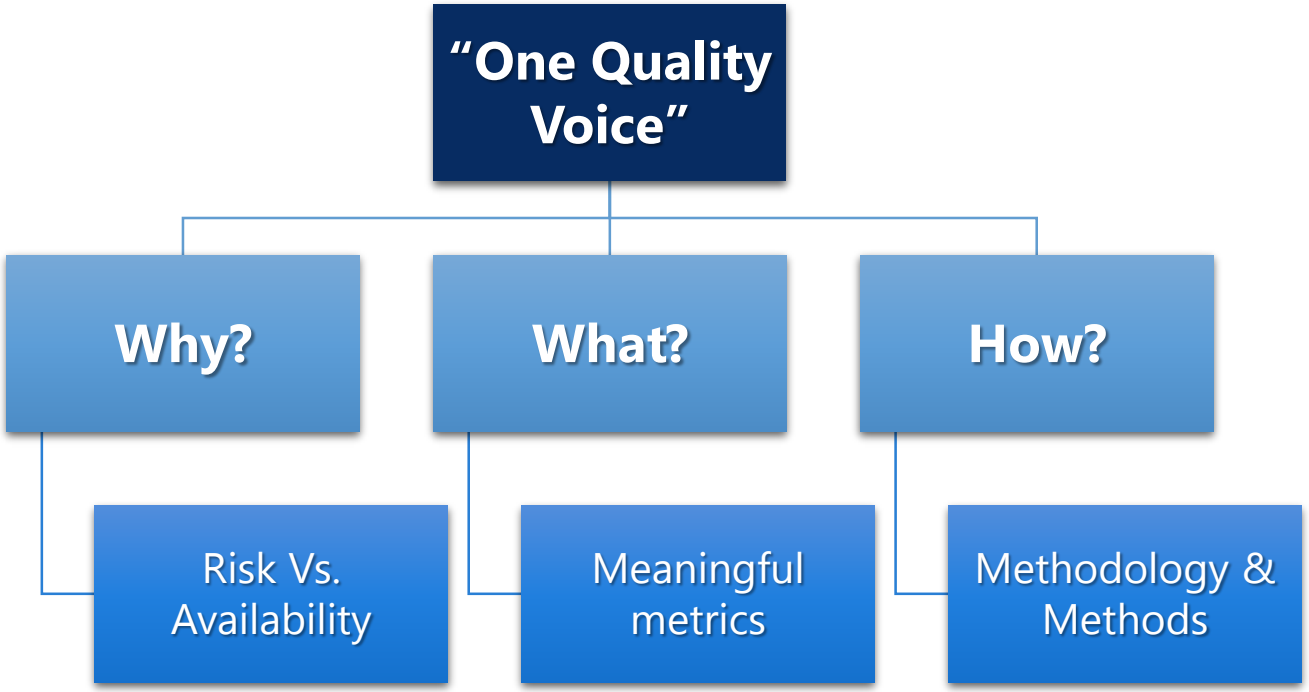
- Continuous Process Verification: An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)
- Continuous Quality Verification (CQV) is described as an approach to process validation where manufacturing process (or supporting utility system) performance is continuously monitored, evaluated and adjusted as necessary". (ASTM E2537-08)
- Continued Process Verification - a stage (Stage 3) of the Process Lifecycle, after Performance Qualification (FDA Process Validation 2011)

"C" in GMP: Current

- Capturing our learning through effective knowledge management
- Plan-Do-Check-Act

Patient relevant





Induce the right behavior and responsibility for industry—Enable better FDA surveillance of the firms' quality state.

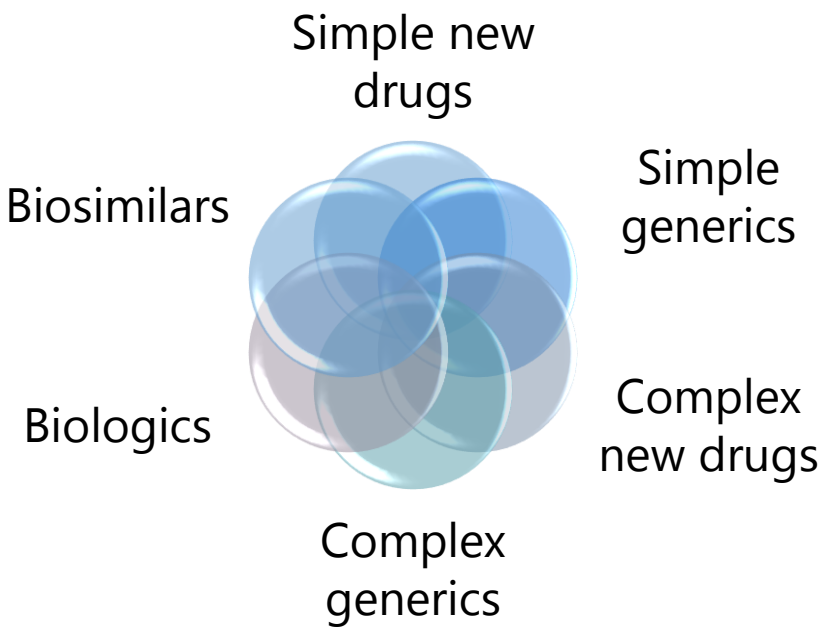
Reduce product-related shortages and quality related recalls—Promote improved product and process capability.

Achieve product quality without extensive regulatory oversight.

Pharmaceutical Quality for the 21st Century: Transformation continues with OPQ

Journey towards science-based risk-assessment & continual improvement; incorporating an integrated approach to quantifiable quality in ways relevant to the patients.

Some questions



- Question based Development to deliver QbD; right Q's?
- Effective alignment for risk-based CGMP Inspections?
- How & when (regulatory) specifications are set?
- Acceptability of process performance and capability?
- Confidence in continued process verification?
- Metrics for effectiveness of CAPA?
- Facility risk-classification & continual improvement?
- ……
- Eliminating the concern of "too good to be true data"?

Role of NIPTE going forward?

NIPTE's focus on interdisciplinary research and education in pharmaceutical technology should positon it well to be a significant contributor for developing "integrated approach to quantifiable quality in ways relevant to the patients."

NIPTE Mission

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

Where does NIPTE want to go next?

The current situation

Near term challenges

Strategic response

What this should mean for NIPTE faculty?

Current Situation?

NIPTE Effectiveness

- What changed 2005:2015
- Advantage to Disadvantage?
- Organization Assessment

FY 2014 GDUFA Regulatory Research Contracts and Grants

Non-oral route

Pharmacometrics

Clinical, VoP

Process modeling

NIPTE; Scope too narrow?

- Characterization of Epilepsy Patients at Risk for Adverse Outcomes Related to Switching Antiepileptic Drug Products • University of Maryland (#HHSF223201400188C)
- Bioequivalence and Characterization of Generic Drugs • Awarded to Vince & Associates Clinical Research, Inc. (#HHSF223201210030I).
- Population pharmacokinetic and pharmacodynamic dose-toxicity modeling and simulation for narrow therapeutic index drugs • University of Maryland, Baltimore (1 U01 FD0005188-01)
- Pharmacometric modeling and simulation for a generic drug substitutability evaluation and post-marketing risk assessment • University of Maryland, Baltimore (1 U01 FD0005192-01) and the University of Florida (1 U01 FD0005210-01)
- Pharmacometric modeling and simulation for pAUC • University of Utah (1 U01 FD0005191-01)
- Dermal absorption • University of South Australia (1 U01 FD005232-01) and Simcyp, Ltd. (1 U01 FD005225-01)
- Ocular delivery • Simulations Plus, Inc. (1U01FD005211-01) and CFD Research Corporation (1U01FD005219-01)
- Complex Drug Products • the State University of New York at Buffalo (1U01FD005206-01)
- Nasal Delivery • Applied Research Associates, Inc. (1 U01 FD005201-01)
- Pulmonary Delivery • CFD Research Corporation (1U01FD005214-01).
- Development of a Clinically Relevant In Vitro Performance Test for Generic Orally-Inhaled Drug Products • the Virginia Commonwealth University (1U01FDD005231)
- Dissolution Methods for Suspension and Emulsion Ocular Drug Products • the University of Eastern Finland (1U01 FD005180-01) and Texas A&M University (1U01 FD005184-01).
- Dissolution Methods for Semisolid Ocular Drug Products • Awarded to the University of Connecticut (1 U01 FD005177-01) and (1U01FD005174-01)
- Dissolution Methods for Microsphere and Implant Drug Products • the University of Connecticut (1U01FD005169-01), Akina, Inc. (1 U01 FD005168-01), and the University of California, San Diego (1U01 FD005173-01)
- Characterization of Critical Quality Attributes for Semisolid Topical Drug Products • the University of Mississippi (1 U01 FD005233-01) and the University of South Australia (1 U01 FD005226-01).
- Evaluation of Plasma NTBI levels in Healthy Subjects Treated with Generic and Reference Sodium Ferric Gluconate • the University of Maryland, Baltimore (1 U01FD005266).
- Effect of Therapeutic Class on Generic Drug Substitutions • to Johns Hopkins University (1U01FD005267-01)
- Post-market Surveillance Evaluation of Authorized Generic Drug Products • Brigham and Women's Hospital (1U01FD005279-1) and Auburn University (1U01FD005272-1).
- Pharmacokinetic/Pharmacodynamic Studies of Generic Cardiovascular Drugs in Hypertensive Patients • the University of Florida (1U01FD005235-01).
- Pharmacokinetic/Pharmacodynamic Studies of Methylphenidate Extended Release Products in Pediatric Attention Deficit Hyperactivity Disorder Patients • the Massachusetts General Hospital (1U01FD005240-01)
- Effect of Different Preparation Methods on the In Vitro and In Vivo Performance of Solid Dispersion Formulations • Purdue University, West Lafayette (1U01FD005259-01)
- Prospective Studies on the Impact of Generic Immunosuppressants on Acute Rejection and Long-Term Graft Survivals • to the University of California, Los Angeles (1 U01 FD005271-01)
- Retrospective Analysis on the Impact of Generic Immunosuppressants on Acute Rejection and LongTerm Graft Survivals • Arbor Research Collaborative for Health (1 U01FD005274-1).
- Evaluation of In Vitro Release Methods for Liposomal Drug Products • ZoneOne Pharma, Inc. (U01FD005249-1).
- Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules • Massachusetts Institute of Technology (U01FD005291-1)
- Development of Process Simulation and Modeling Tools for Integrated Pharmaceutical Manufacturing Processes • University of Massachusetts Lowell (U01FD005294-01) and Rutgers (U01FD005295- 01)
- Establishing Specifications to Assure the Quality of the Heparin Supply Chain • G Ronzoni Institute for Chemical and Biochemical Research (HHSF223201400578P)

Organization Assessment

S

Strengths

- Track-record of delivering proposals and results
- Several mature projects, can be leveraged to expand NIPTE's offerings
- Commitment and dedication of 'core' faculty leaders and of Board Members

W

Weaknesses

- Funding only from FDA; uncertainty increased
- Stakeholder perceptions/questions on 'impact'
- Strength of the collective not effectively leveraged and/or showcased

O

Opportunities

- Research core - formulation design increasingly critical for nano-, pediatrics, and individualized therapies
- Need for NIPTE remains; education and advocacy for science remains untapped
- Vacancy -"Independent Voice for the Patients"; interested?

T

Threats

- Dwindling passions beyond the 'core'; core shrinking?
- Increased funding opportunities for individual faculty projects
- Other consortia and collaborations; what is unique about NIPTE?

Going forward: NIPTE building on its strengths

- Integrated solutions for supporting needs of FDA and industry

Examples of strategic response…..

NIPTE Beyond 2015

Improving NIPTE- FDA collaboration

Expanding collaboration capabilities

Training programs for Industry

Knowledge based business decisions

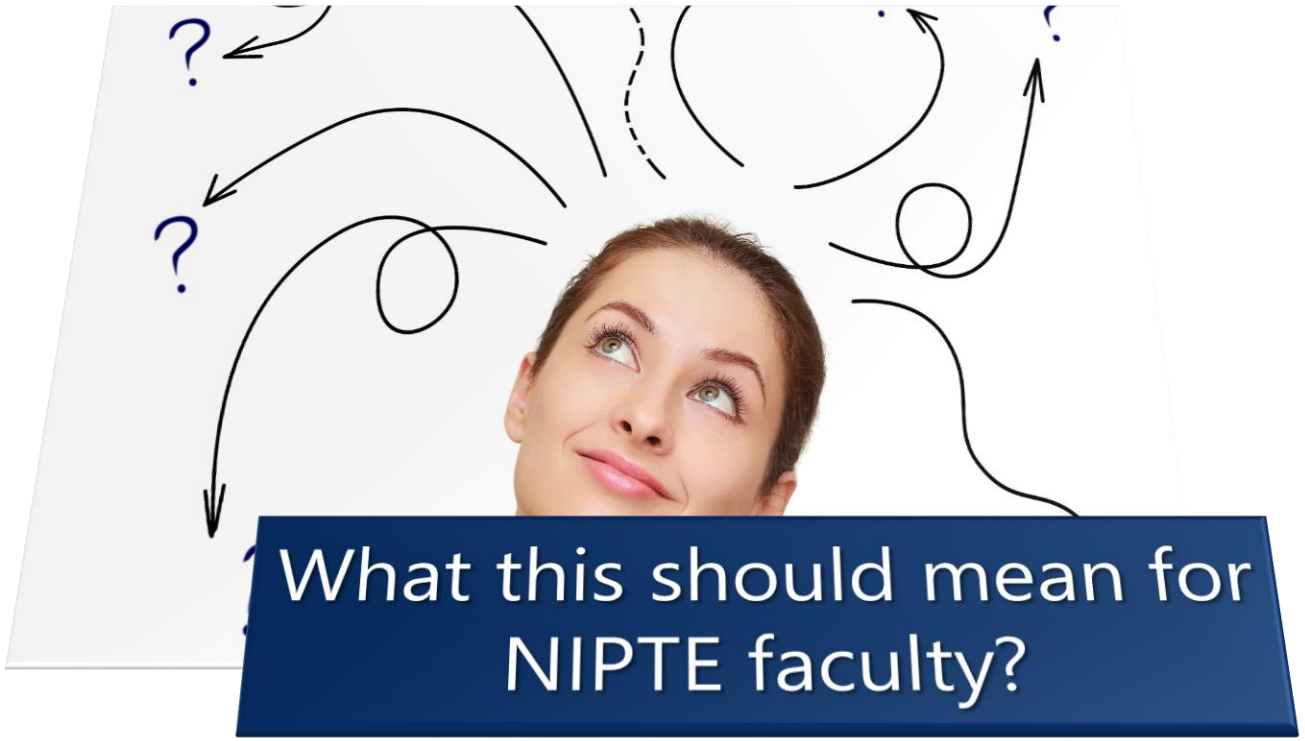
Illustrative projects (initiated or under discussion)

(1) Ways to improve impact of FDA UO1 & (2) Reviewer training program – lessons learned

(1) University of Rochester Medical Center (URMC) & (2) Adding Pharmacometrics and Econometrics dimensions

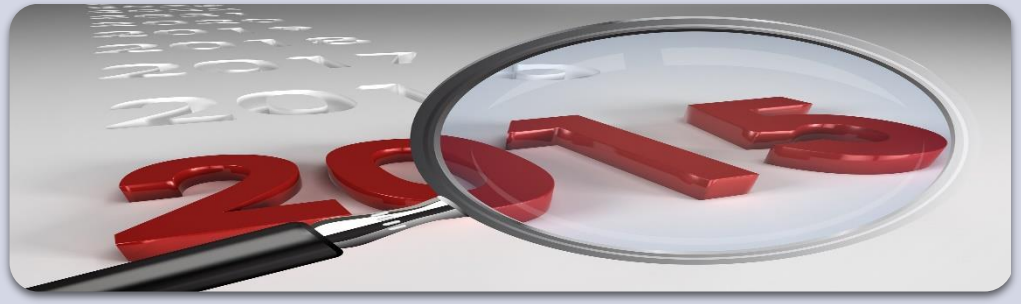
(1) MoU for training with Sun Pharma Ltd. & (2) Scalable, sustainability model – funding for faculty

(1) Business case for NIPTE Excipient Knowledge Base & (2) Support for investment in continuous manufacturing



- Improve leadership opportunities
- New opportunities to ‘connect-the – dots’; multidisciplinary
- Improve ability to serve the patients and the Nation
- Sustainability and predictability of NIPTE

Concluding remarks



Collaboration with FDA has sustained NIPTE for a decade and helped it to develop a system for the faculty to serve the patients and the Nation through their research and training on how to improve affordability of medicines & enhancing confidence in its quality.

Clearly there is now an urgent need to expand our efforts to improve affordability of medicines & to enhance confidence in quality. NIPTE will continue to seek to improve its collaboration with the FDA while it expands its programming to collaborate with industry – consistent with its mission and not-for-profit status.

Concluding remarks

NIPTE remains an expression of interest by, and a system to collaborate for, a group of fiercely independent 'pharmaceutical technology' faculty who wish to predictability sustain their research and graduate programs. This is one expression of their passion for public service.

NIPTE is committed to sustain this passion and to provide an effective system for the faculty to serve the patients and the Nation through their research and training contributions that measurably improve affordability of medicines & enhance confidence in quality.