

How the Restructuring at the FDA is Affecting How Submissions are Reviewed and How they Need to be Submitted”

Panel Discussion

David Lin, Ph.D. & Duu-Gong Wu, Ph.D.

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Topics for Panel Discussion

- Organizational changes from ONDC to ONDQA
- Changes in the internal CMC review process
 - INDs, NDAs, Supplements,
 - Responsibility of ONDQA personnel
- Revisions and recent withdrawal of domestic guidance documents
- How to adopt the new organization and process for CMC submissions
- Specific issues related to IND/NDA submissions under new organization
- How are applications for biologic products being handled and reviewed?

Outline

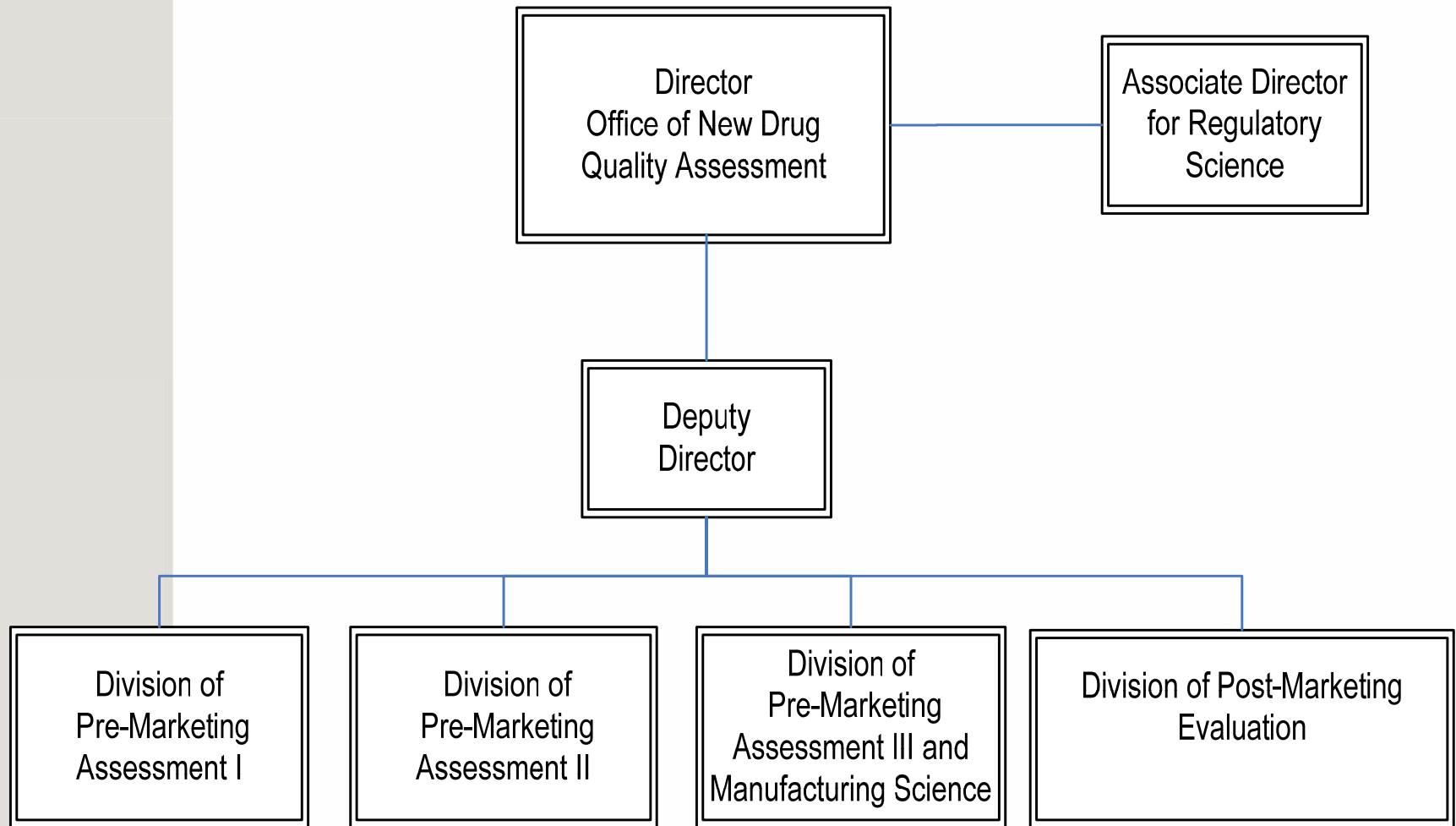
- Background
- Organizational changes from CDER Office of New Drug Chemistry to Office of Office of New Drug Quality Assessment
- Changes in the internal CMC review process and practices
- Revisions and recent withdrawal of domestic guidance documents

A Product Quality System for the 21st Century

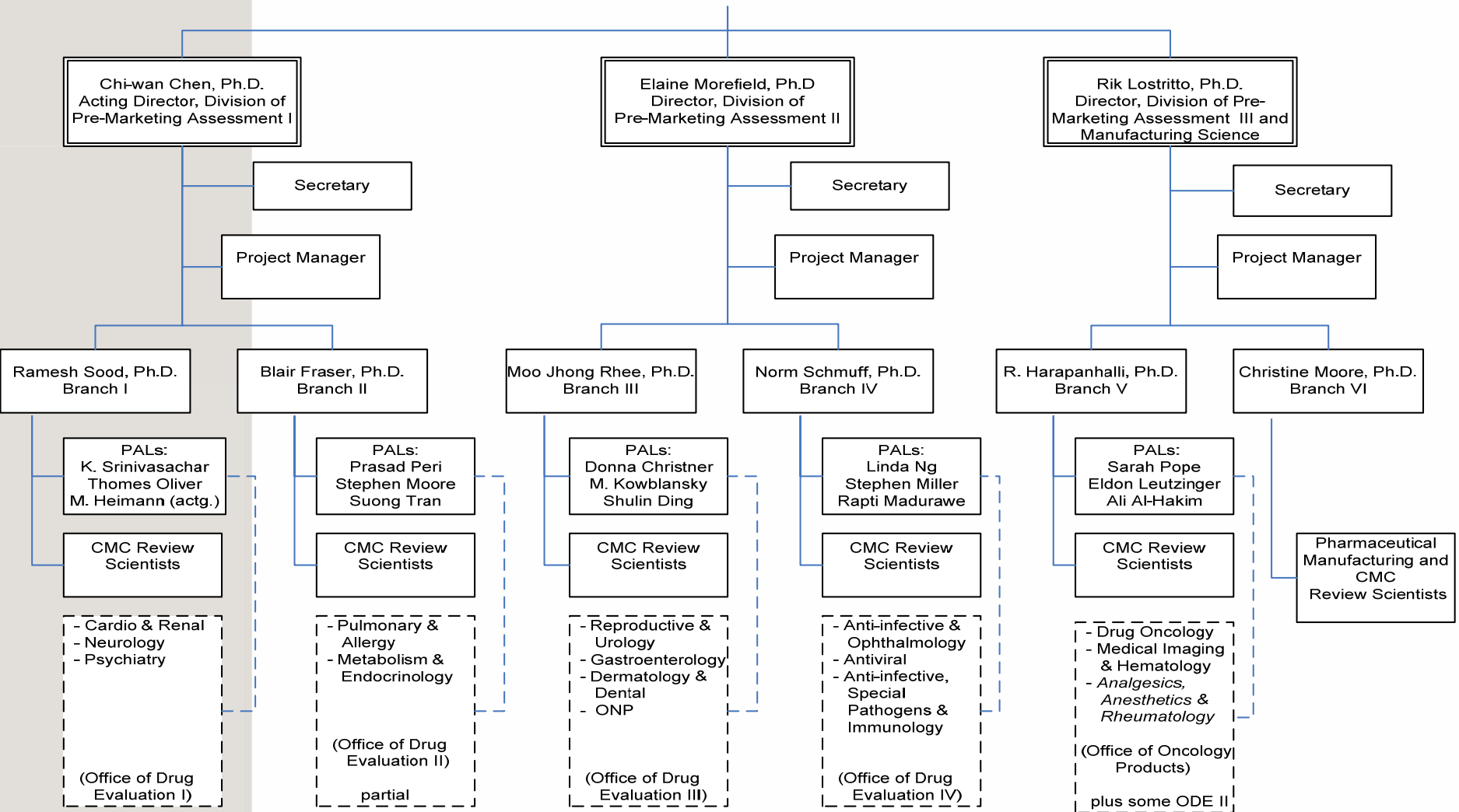
- Risk Management (priorities, resource allocation and setting regulatory requirements)
- Science-based regulatory approaches (conduct scientific risk assessment and facilitate technological advances)
- Strong public health focus
- International cooperation
- Assessment and implementation of appropriate quality management systems
- Integrated product quality regulatory practice (review and inspection processes)

Moheb M. Nasr, Ph.D., DIA, 2004

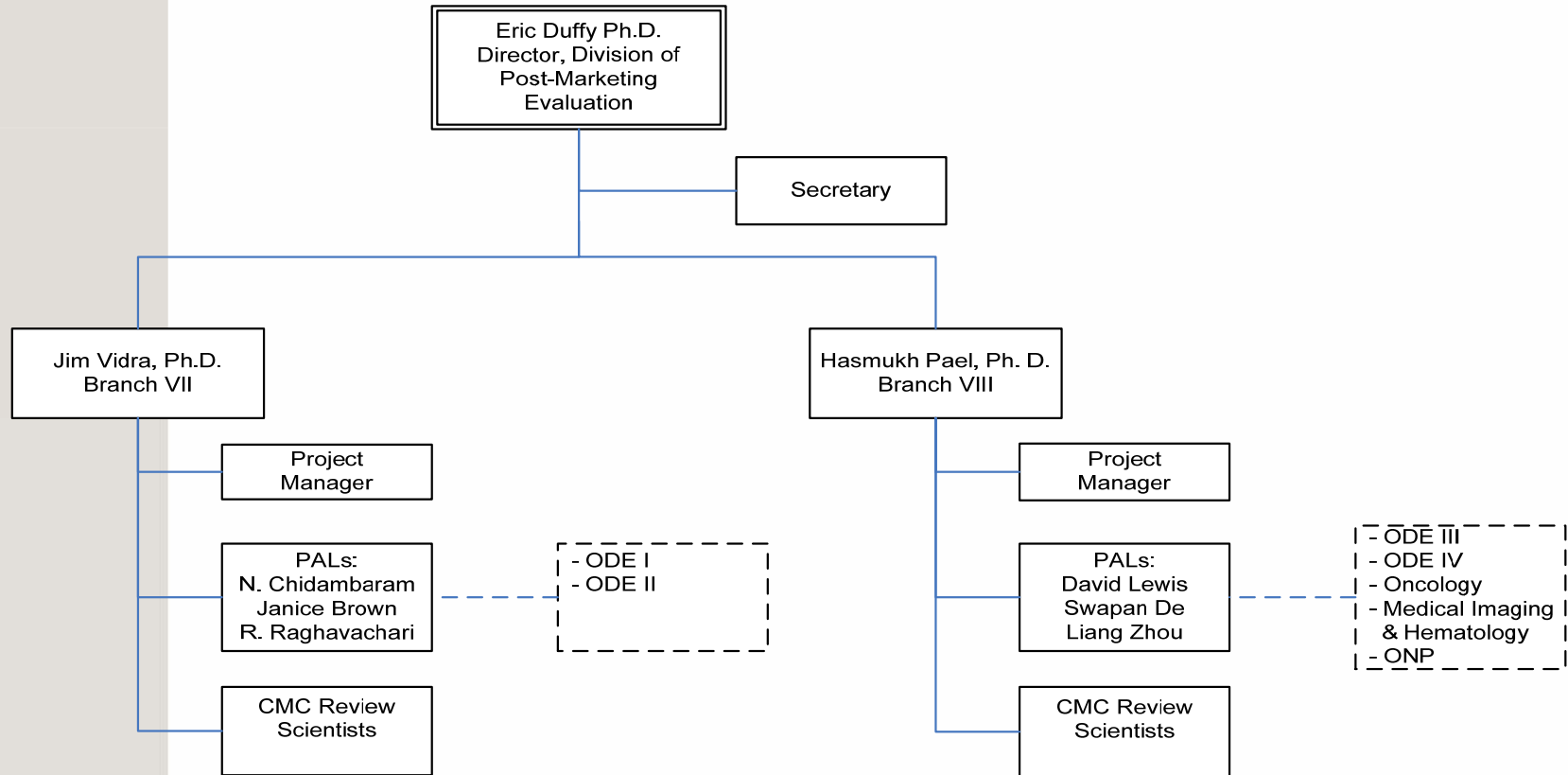
New ONDQA Organization



Pre-marketing and MS Divisions



Post-Marketing Evaluation

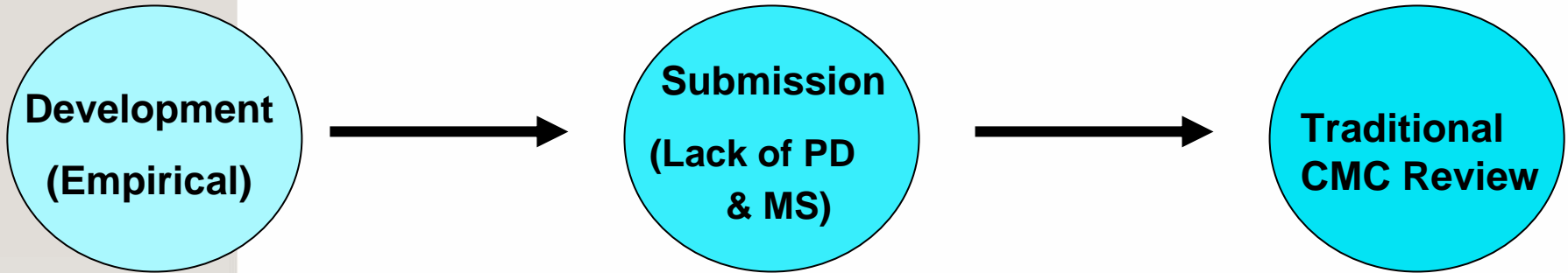


ONDQA Restructuring

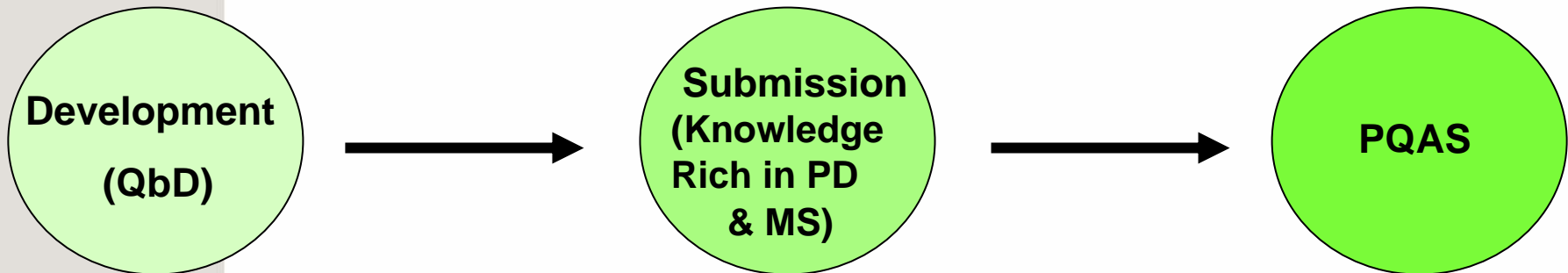
- Pre-Marketing divisions to focus on INDs and NDAs to facilitate risk-based review
- Post-Market Division to focus on post approval issues
- Streamlining CMC Review
- Triage of supplements based on risk prior to review assignments
- Reduction of prior approval supplement
- Introduction of manufacturing science into review process
- To implement the new Pharmaceutical Quality Assessment System (PQAS)

Pharmaceutical Quality Assessment System

Current System



Desired State



PQAS – Submissions

- Streamlined submissions
 - Relevant scientific information and analysis (e.g., summaries, tables and graphs)
 - No irrelevant, redundant, or raw data
- Pharmaceutical Development Information
- Comprehensive QOS, possibly as the “main” review document
- Relevant product and manufacturing process design information
- Applicants’ assessment/analysis included in submission (old EU Expert Reports)

Implemented Changes

- ONDC to ONDQA and re-organization
- Separations of pre-marketing and post-marketing as well as manufacturing process reviews
- No co-locations with clinical divisions
- PAL for initial reviews and assignments; Branch Chiefs for sign-offs
- Flexible assignments and team review
- Risk-based decisions on supplement categories and use of comparability protocols
- Focus on pharmaceutical development and QOS
- Withdrawal of DS, DS, and Stability guidances
- Pilot programs for QbD applications
- Others such as GMP inspections by chemists (where is PAT?)

PQAS Review

- No more single reviewer for the life cycle of a product
- Assesses pharmaceutical development for product and process
 - Evaluates scientific rationale used to support the selection of CPPs and in-process controls
 - Links material properties and critical steps to CQAs of DS, DP and intermediates
- Identifies critical quality attributes for DP, DS, and excipients based on DP quality, performance, stability, and manufacturing process
- Evaluates suitability of formulation

Process of CMC Pilot Program

- Potential participants will discuss plans with ONDQA
- Once accepted, participants can meet with ONDQA as frequently as needed
- Assessment will be conducted by a team of experienced reviewers with good understanding of the new PQAS and strong background in PD and manufacturing processes
- Team Review overseen by ONDQA Director
- Participation of ORA and CDER's compliance (Review & Inspection Team)
- *Moheb Nasr, ONDQA, FDA*

New Supplement Review Process

- Supplement triage to identify:
 - Low risk changes
 - Moderate risk changes
 - Changes critical to product performance
- Low risk
 - supplement not needed
 - AR - identify categories of such changes
- Moderate risk – expedited brief review
- Critical changes – comprehensive review

Guidance Withdrawal

- 1987 Content and format
- Draft Drug Substance and Drug Product (CTD-Q), 2004
- Stability
- Synthetic Peptide
- BAPAC I
- cGMP for Phase 1 final rules
- Others to follow?

Terms to be Familiar with

- **Quality Overall Summary**-Concise compilation of product information that follows the scope and outline of the Body of Data in CTD Module 3. It should provide sufficient information to allow an overview and quality assessment of the product - emphasizing critical parameters of the product and should integrate and cross reference critical information appropriate sections of the submission. It should including tables, figures, or other items that summarize raw data.
- **Comparability Protocol** - A comprehensive plan for assessing the effect of specific CMC changes on the identity, strength, quality, purity, and potency of a drug product as they may relate to the safety and effectiveness . The plan describes changes that will be performed, including the attributes that will be used to demonstrate that specified CMC changes do not adversely affect the product.

Terms to be Familiar with

- **Quality by Design-** A systematic process of building desirable quality by a careful evaluation of all the attributes that go into characterizing quality, from the inception of a product to its end use.
- **Pharmaceutical Development -** Collected information on development studies conducted to establish that the dosage form, the formulation, manufacturing process, quality attributes are appropriate for the product. It should identify and describe the formulation and process attributes (critical parameters) that can influence product quality and performance)

Space

- **Design Space** – Multi-dimensional region that encompasses combinations of product design, manufacturing process design, manufacturing process operating parameters and raw material quality that produce material or product of suitable quality and Fit for Use.
- **Knowledge Space** – Compilation of all previously learned facts about a process.
- **Control Space** - Multi-dimensional region that encompasses process operating parameters and raw material quality measurements that assure process or product quality.
- **Edge of Failure** – the outer regions of a design space where critical process parameters, critical product attributes and performance place the fitness of product use at its maxima.

Manufacturing

- **Quality System(s)** – Describes how a firm defines, enacts and maintains a state of compliance and control as well as the management governance, responsibilities and roles that oversee product management.
- **Science-based GMP(s)** – Product compliance through establishment of scientifically sound and appropriate acceptance criteria, standards, sampling plans, and measuring/monitoring procedures designed to assure that components, in-process materials, and drug products conform to appropriate quality attributes for identity, strength, quality, and purity.

Contact Information

David T. Lin, Ph.D.

Senior Consultant

**Biologics Consulting
Group, Inc.**

Alexandria, VA

1317 King Street

Alexandria, VA 22314

dlin@bcg-usa.com

Tel: (301) 299-2853

Duu-Gong Wu, Ph.D.

**Executive Director,
PharmaNet**

**815 Connecticut Avenue,
NW, Suite 800**

Washington, DC 20006

dwu@pharmanet.com

Tel: (202) 835-1341