Manufacturing Process and Controls:

How to Avoid Major Review Issues Turning into Potential Deficiencies

Nallaperumal Chidambaram, Ph.D.
Branch Chief (Acting)
Division of Process Assessment III
Office of Process and Facilities (OPF)/OPQ/CDER/FDA

CDER Small Business and Industry Assistance
Regulatory Education for Industry
Generic Drugs Forum 2017
Silver Spring, Maryland
April 4 – 5, 2017

Outline

- Introduction
- Organizational Structure
- Role of Manufacturing Process
- Common Major Deficiencies
- Case Studies
- Conclusions and Recommendations

Early 2000s: FDA Embarks upon Pharmaceutical Quality for 21st Century Initiative

Vision

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight."

-Dr. Janet Woodcock

OPQ Mission, Vision & Slogan

Mission

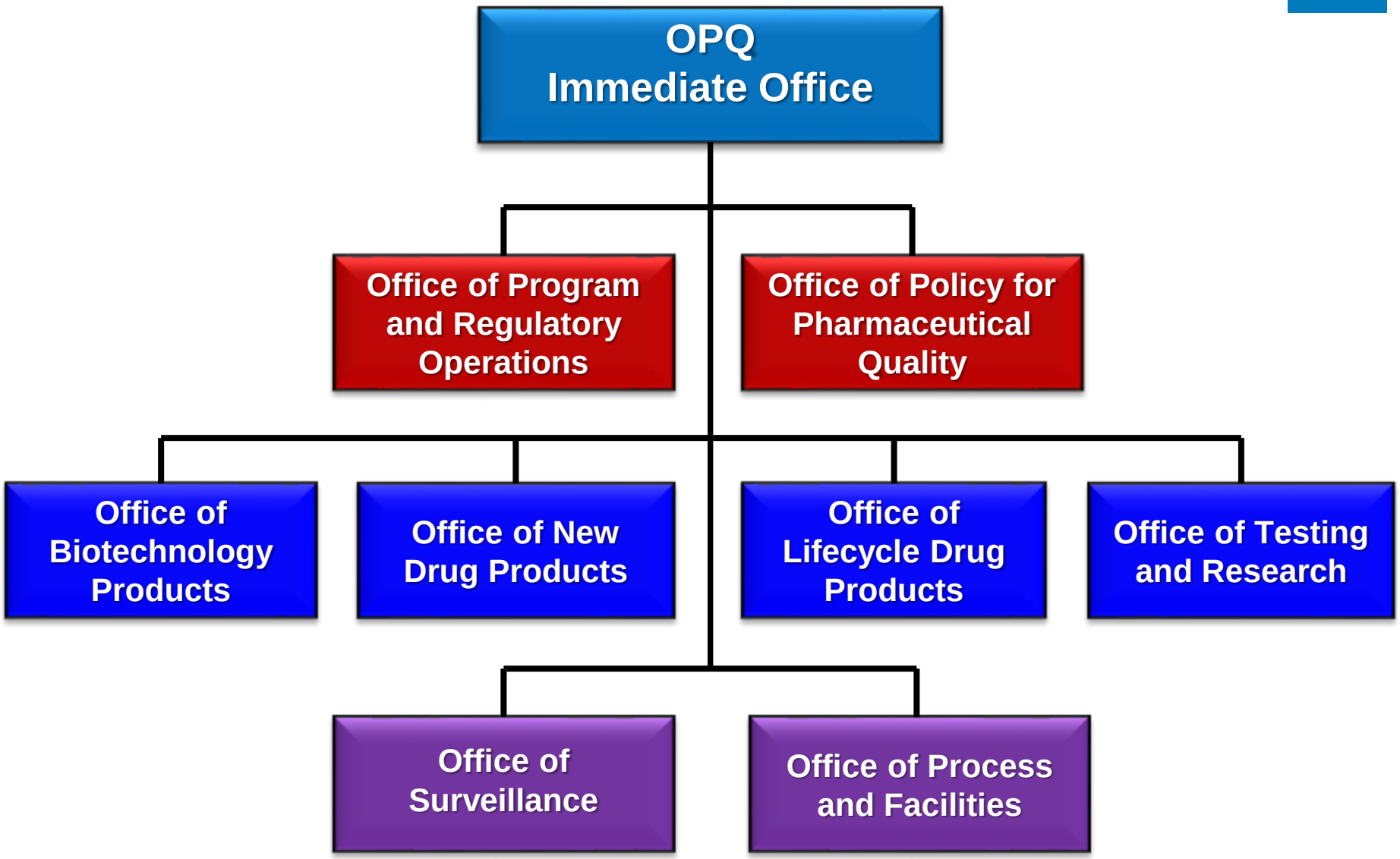
The OPQ assures that quality medicines are available to the American public

Vision

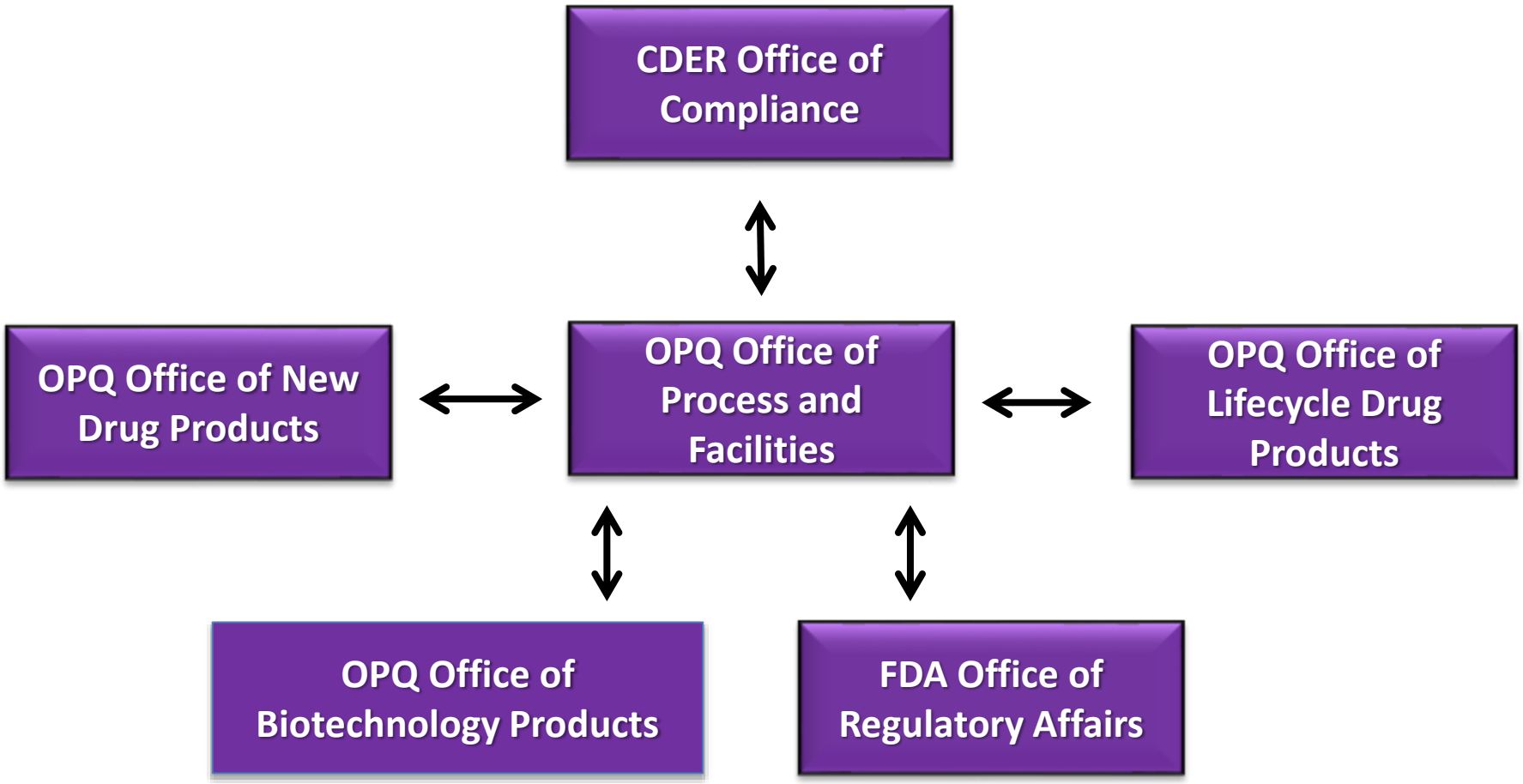
The OPQ will be global benchmark for regulation of pharmaceutical quality

Slogan

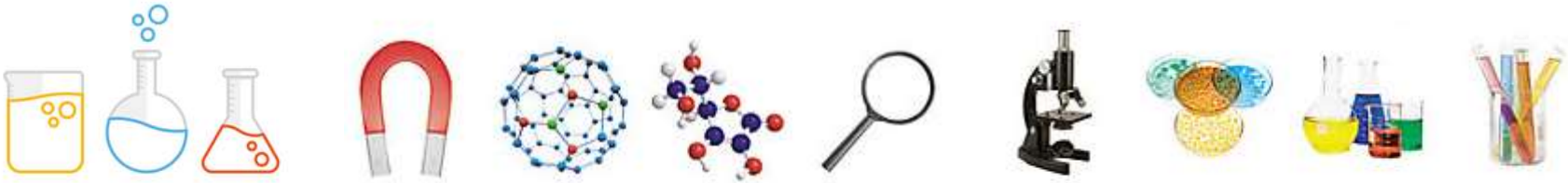
‘One Quality Voice’


OPQ
Immediate Office
Office of Program and Regulatory Operations
Office of Policy for Pharmaceutical Quality
Office of Biotechnology Products
Office of New Drug Products
Office of Lifecycle Drug Products
Office of Testing and Research
Office of Surveillance
Office of Process and Facilities

Office of process and Facilities



Product Quality



How does it link to the patient?

Expectations for Quality

Patients and caregivers assume that their drugs:

- Are safe, efficacious, and have the correct identity
- Deliver the same performance as described in the label
- Perform consistently over their shelf life
- Are made in a manner that ensures quality
- Will be available when needed

Patient

Quality Target Product Profile

Product

Critical Quality Attributes

Process

Material Attributes & Process Parameters

Common Major Deficiencies

- Change in Morphic Form of the drug Substance – Impact on Drug product CQAs
- New Source of API submitted in an Amendment
- API – Excipient Interaction
- Use of <2 lots of API to Manufacture 3 exhibit batches
- Significant Differences in the Information provided in Module 2 and Module 3
  - Process Description, In-process Controls, Scale Up Information

Common Major Deficiencies
(Contd)

- **Inclusion of New Drug Product Strength in the Amended Application**
- **CPPs are indicated as TBD during Process Validation**
- **Data Integrity**
- **Scale Up Dissolution Failure**
- **Change in Dissolution Acceptance Criteria for an ER Product**

Common Major Deficiencies
(Contd)

- Manufacturing site change
- Change in Granulation process
- Differences in Manufacturing Process proposed for Exhibit/Commercial Batches
- Scale Dependent CPPs not adequately Justified
- Use of excess overage

Case Study 1

Change in Morphic Form of the drug Substance – Impact on Drug product CQAs

Process Risk vs Physical Stability

- **Spectroscopic data to show no change in the API morphic form through manufacturing & Shelf-life**
- **Analytical method suitability**

Case Study 2

Use of <2 lots of API to Manufacture 3 exhibit batches per ANDA Stability Guidance

Requires manufacturing of a new batch

- **-Satisfy the Stability Guidance**
- **-Stability Failure**

- **Considerable amount of time required to review submitted data in the amendment**

Case Study 3

Change in Dissolution Acceptance Criteria for an Extended Release Product

Modification to coating process parameters, coating thickness

- **Require new batches to be manufactured**

❖ **Considerable amount of time required to review submitted data in the amendment**

Case Study 4

Change in Granulation Process

Dry Granulation vs Wet Granulation

Granulation process selected

- **Justified with data**
- **Risk mitigation strategy**

Case Study 5

Master Batch record

Differences in Executed Batch vs. Commercial Batch

- **Variation in Equipment % Utilization**
- **Differences in Manufacturing Process**
- **Low Yields not Justified**
- **Hold Times not Justified**

Conclusions and Recommendations

- Develop a thorough product and process understanding
- Establish adequate material controls, Critical Process Parameters, In-process controls
- Establish Design and Operating Process Ranges with appropriate in-process controls
- Justify any observed differences
- Provide all required information and supportive data
- A complete and comprehensive submission will facilitate first cycle approval

Acknowledgements

- Robert Iser
- Naiqi Ya
- Ubrani Venkataram
- Yaodong Huang
- Erin Kim
- Yuesheng Ye

Thank you!

Please complete the session survey:

surveymonkey.com/r/GDF-D2S13