CMC Initiative Development for New and Generic Drugs

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GPhA/FDA CMC Workshop
June 4-5, 2013

Outline

- Integrated Team-based Quality Assessment
- Question-based Review
- Electronic Submission of Drug Master Files
- Product Quality Informatics

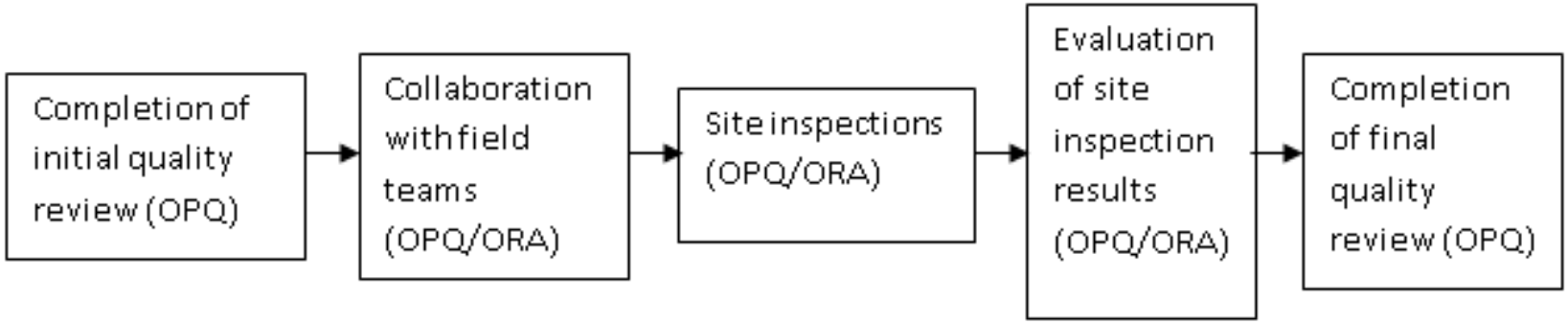
2012 GPhA Fall Technical Workshop

- Formation of DMF review staff
- Focus on the evaluation of Type II DMFs
- Separate drug substance and drug product review to enhance the quality, efficiency, and consistency of the evaluation
- Immediate impact by GDUFA

Integrated Team-based Quality Assessment

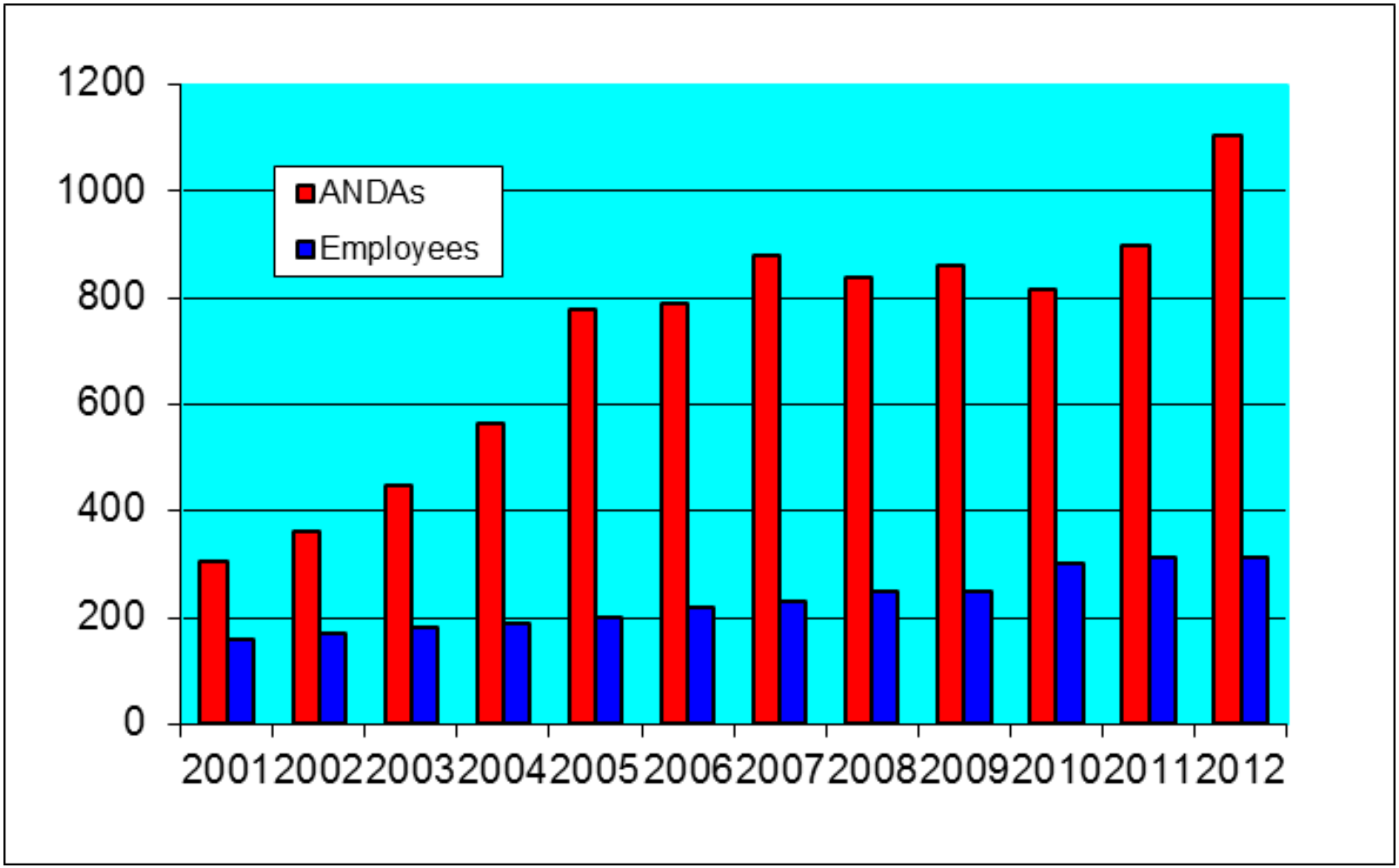
- Integrated Team-based Quality Assessment
  - Drug substance reviewer,
  - Drug product reviewer,
  - Compliance process reviewer/officer,
  - Microbiology reviewer, and/or
  - Drug release reviewer
- A pilot was conducted to evaluate its feasibility, effectiveness, and efficiency

Integration of Review and Inspection



Challenges: Timing, timing, and timing…

Generic Applications versus Employees



Risk-based Assessment

- Failure mode analysis
- Risk to patients and risk of manufacturing
  - Low risk
    - "Abbreviated" yet appropriate review
  - Medium risk
    - Regular review
  - High risk
    - Extra scrutiny to reduce risk

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Question-based Review

- Question-based Review (QbR) is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to
  - Set regulatory standards relevant to clinical performance (safety and efficacy)
  - Assess applicants' understanding and control of product and manufacturing

Janet Woodcock
The Concept of Pharmaceutical Quality
Am. Pharm. Rev. (2004)

"Risk is the concept that can connect the desired clinical attributes—clinical performance as labeled, absence of contamination, and availability—to attributes measurable during production. To make that link, we must turn to the science of manufacturing and the concept of *quality by design* (QbD), which means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches."

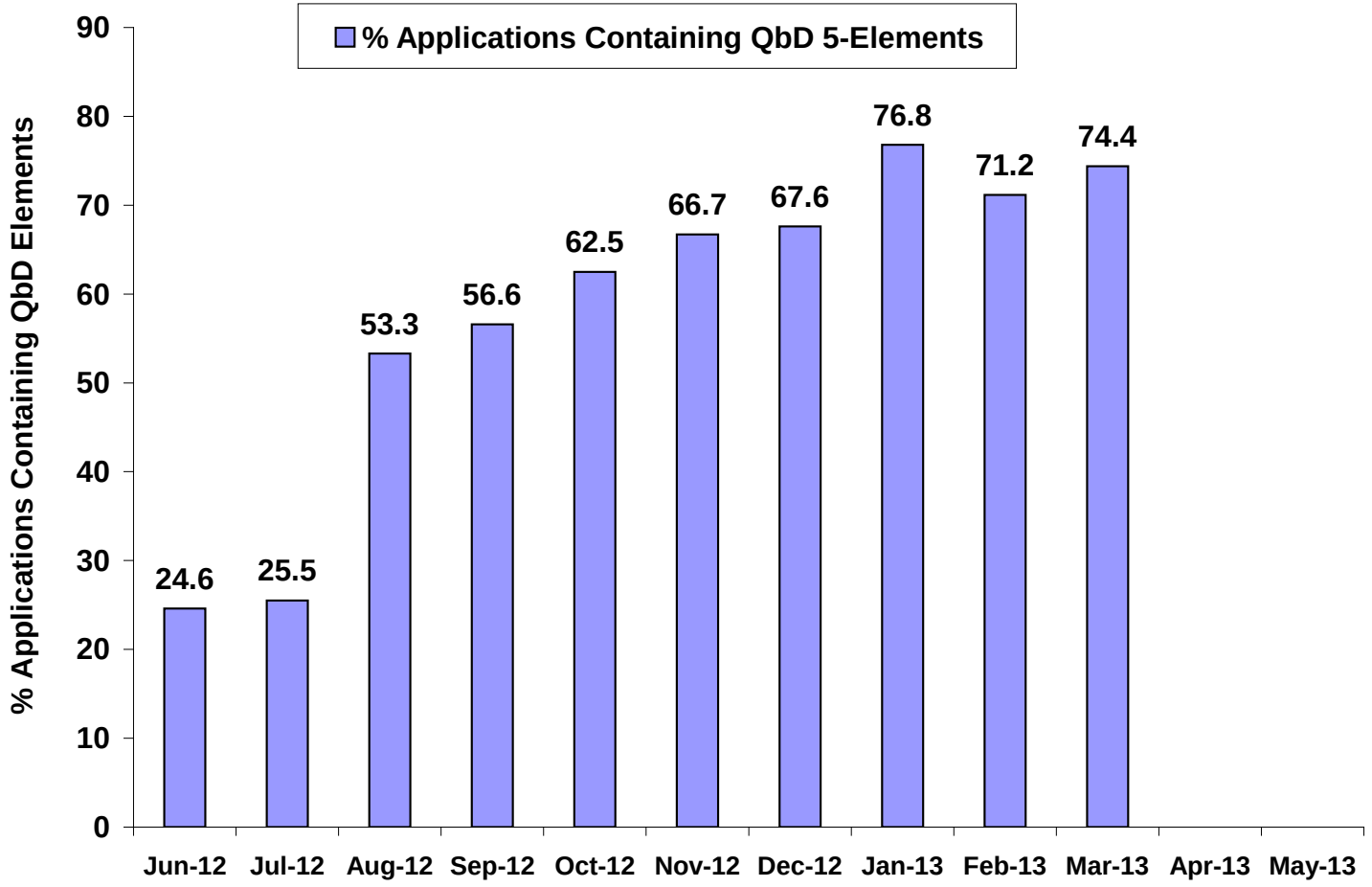
Quality by Design (QbD) and Question-based Review (QbR)

FDA's Pharmaceutical Quality for the 21st Century
QbD Initiative, ICH Q8, Q9, and Q10

Generic Applicant:
Implementing QbD in development, manufacturing, and control

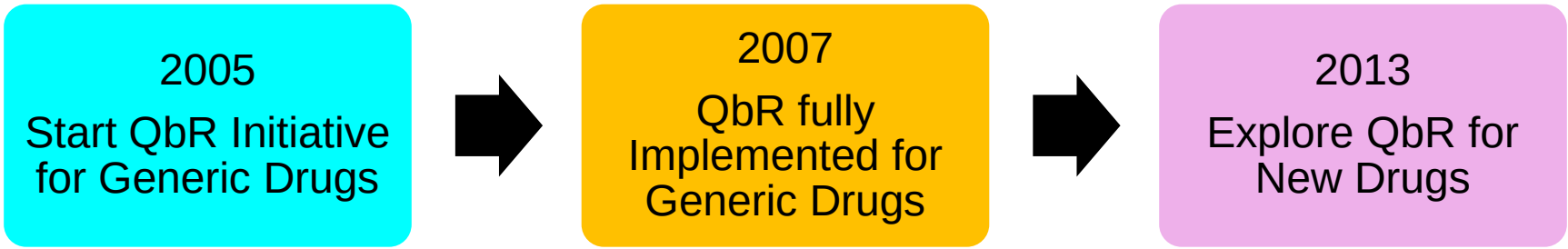
FDA OGD:
Developed a QbR System that assesses applicant's QbD ANDAs

QbD Implementation Status in Generic Industry



Based on brief inspection of Pharmaceutical Development Reports

QbR Evolution



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ANDAs Under QbR
(2005 GPhA Fall Technical Workshop)

- The 1999 Guidance for Industry "Organization of an ANDA"
  - Does not include Quality by Design principles
  - Does not provide for a QoS
  - Is no longer current for the OGD Question-based Review
- Future Generic Applications
  - We strongly recommend that generic sponsors submit generic applications based on the format of ICH CTD, preferably, electronically

Electronic Submission of Drug Master Files (DMF)

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- Question-based Review
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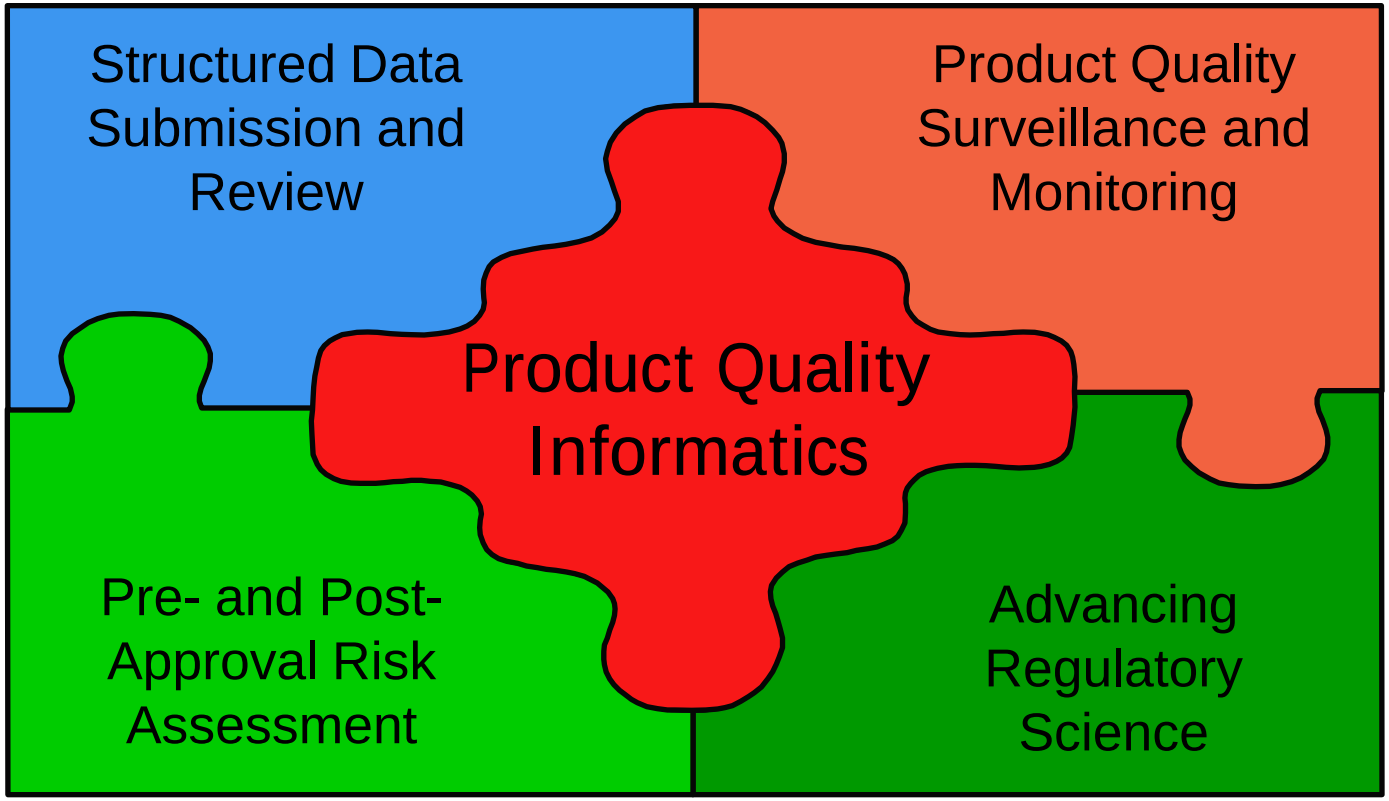
Future Quality Review Office Should Provide

- Seamless review and surveillance from evaluation of product design and quality standard, through evaluation of process and manufacturing facility, to product quality surveillance
- Assurance that all human drugs meet the same standards of quality
- Balance between pre-marketing evaluation and post-marketing surveillance
- Transformation of product quality monitoring from a qualitative to a quantitative process

Product Quality Informatics



Structured Data Submission and Review

- Data standards for submission and review of quality information need to be established in a harmonized way that facilitates the capture of quality information
  - drug substance physical, chemical, and biopharmaceutical property
  - drug substance synthesis and control
  - drug substance standard including analytical method
  - BCS classification (including solubility data)
  - therapeutic category

Structured Data Submission and Review (continued)

- dosage form and formulation composition
- pharmaceutical development information
- product manufacturing process and control
- container closure information
- product and excipient quality standard including analytical method
- Data on manufactured batches
  - Manufacturing site
  - Quality data including release and stability when appropriate

Product Quality Surveillance

- The hallmark of the quality surveillance is real-time compliance in which manufacturers provide electronic summaries of product quality to FDA
  - Continuous monitoring to identify trends that indicate problem within a product class and/or a manufacturer to reduce drug shortage
  - Particularly important as globalization
  - For-cause inspection

Advancing Regulatory Science

- Structured quality data will allow the evaluation of effect of excipients on manufacturability and performance
- Process modeling, simulation, and control
- Predictive models of process scale up
- Multivariate data analysis for characterization of complex drug substance and drug product
- Correlation of product quality with dissolution, bioavailability, and bioequivalence

- Product surveillance
- Optimization studies
- Continual improvement

- Robust QMS
- Quality metrics
- Surveillance model

"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight"

- New quality and surveillance model: Process verification
- Timing of PAI

- Abbreviated review
- Reduced PAS
- For cause inspection

- New quality oversight
- Performance standard
- "Real time" compliance
- Quality metrics

Summary

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