


U.S. Department of Health and Human Services
Food and Drug Administration


Question-based Review for Generic Drugs

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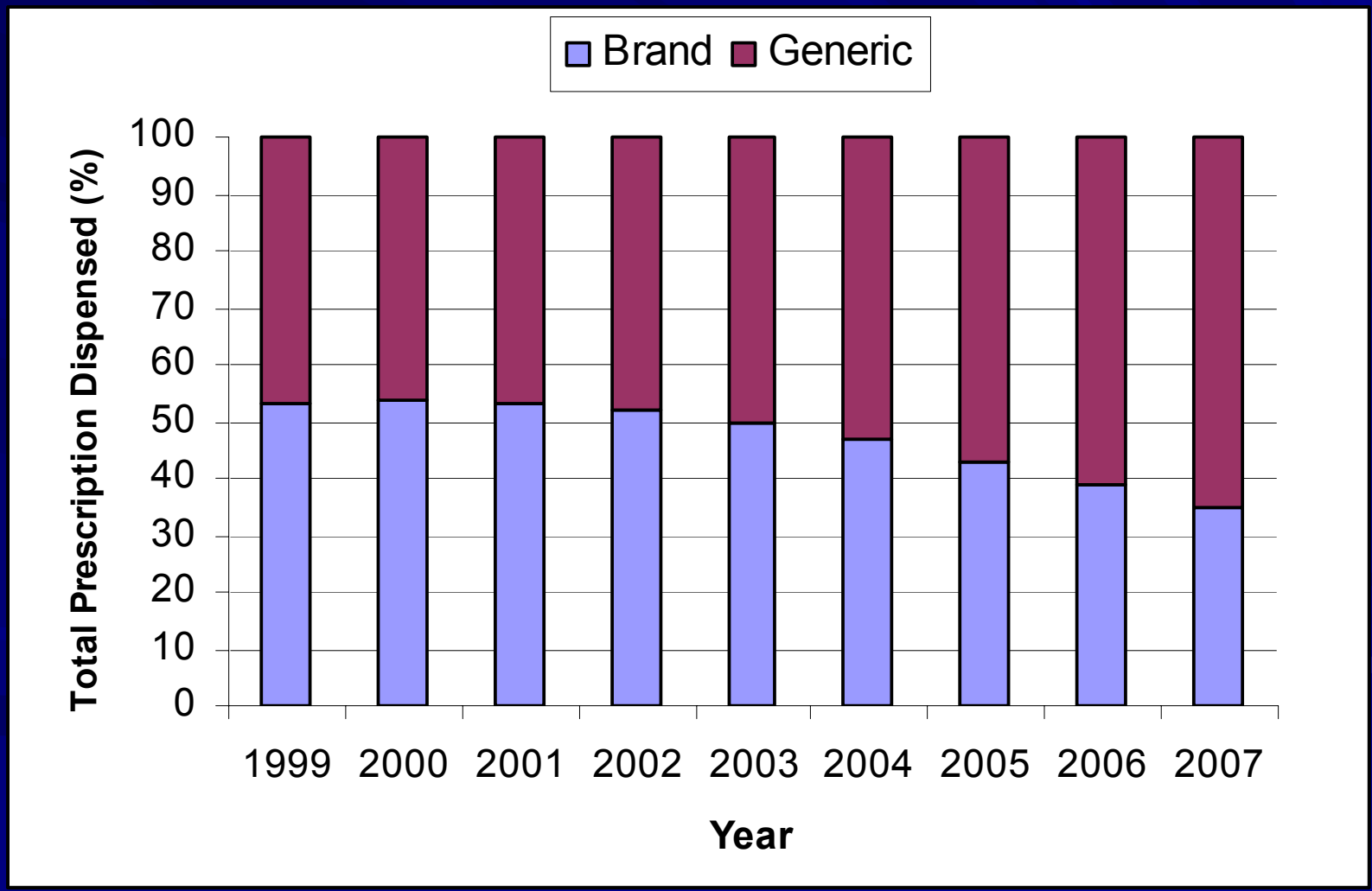
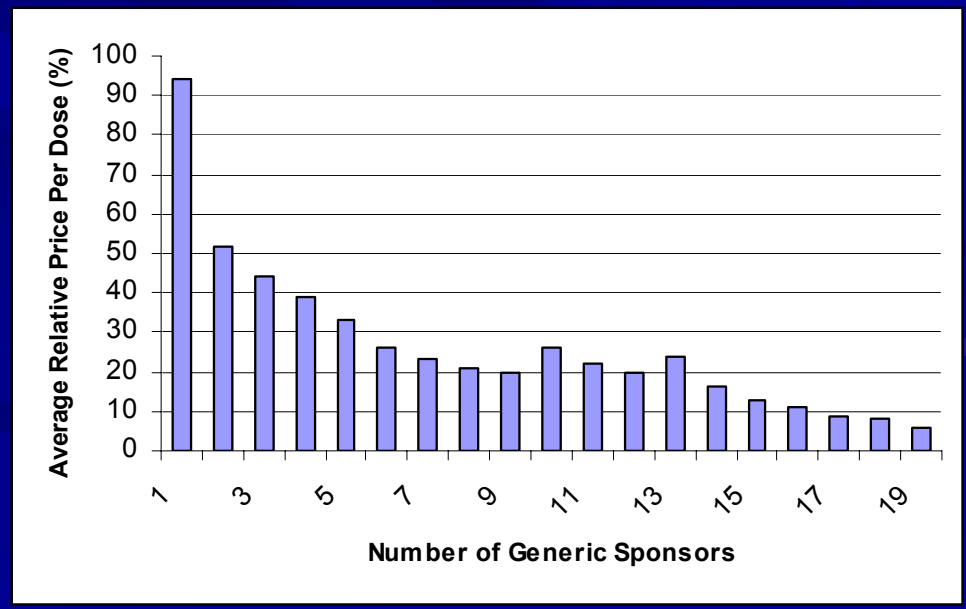
Total Prescription Drugs Dispensed in the United States



Generic Drug Price

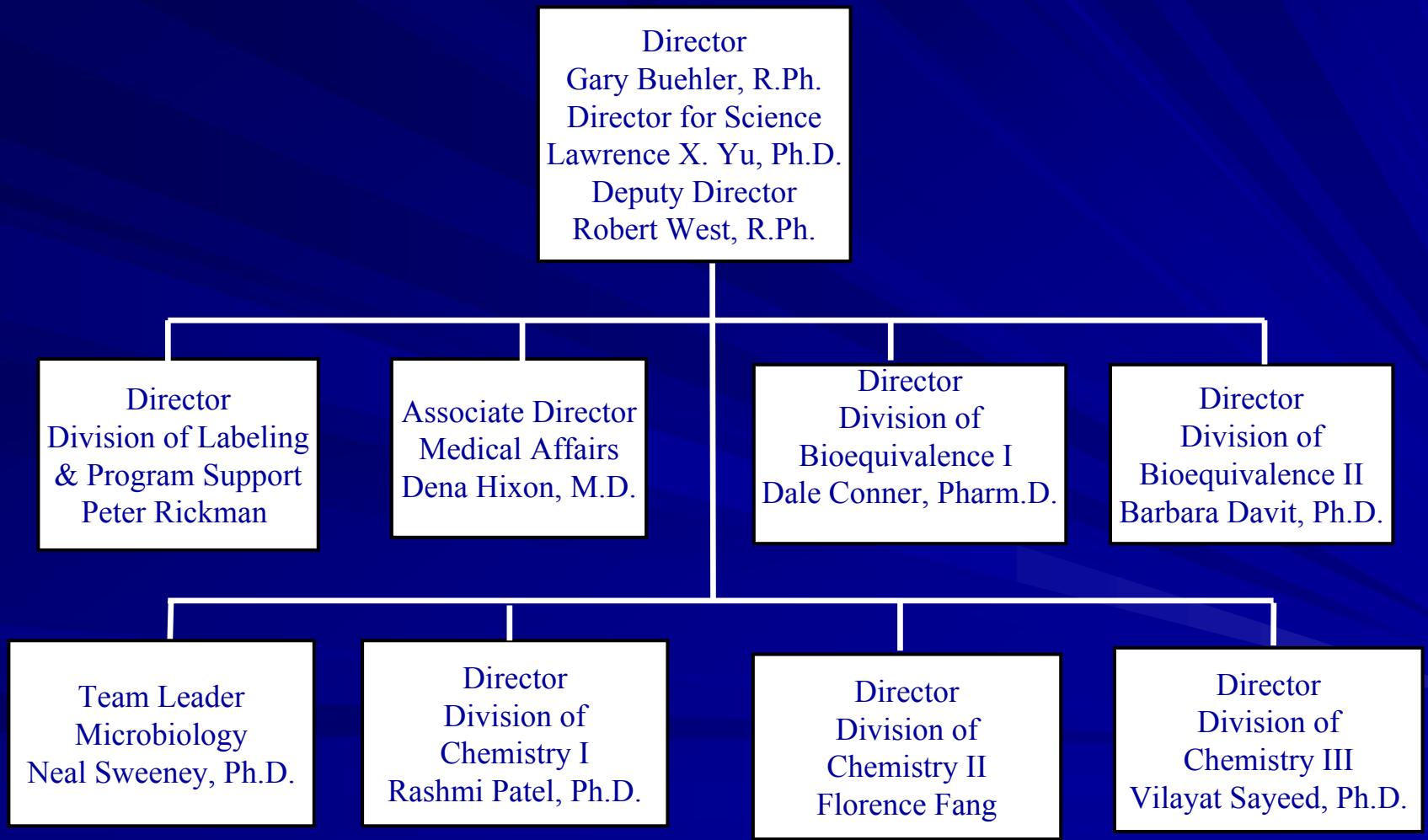
- In 2007, the U.S. generic drug sales have reached $58.5 billion
- In 2006, the average retail price of a generic prescription drug was $32.23 while the average retail price of a brand name prescription drug was $111.02.



Drug Price Competition and Patent Restoration Act of 1984

- Provisions for extending the term of a patent to reflect regulatory delays encountered in obtaining marketing approval by the FDA;
- a statutory exemption from patent infringement for activities associated with regulatory marketing application. Thus, generic sponsors may start to work on a generic version of an approved brand name drug any time during the life of the patent, so long as that work furthers compliance with FDA regulations;
- establishment of mechanisms to challenge the validity of a pharmaceutical patent; and a reward for disputing the validity, enforceability, or infringement of a patented and approved drug; and
- the FDA's certain authorities to offer periods of marketing exclusivity for a pharmaceutical independent of the rights conferred by patents.

FDA OGD Organization



FDA OGD Mission, Vision, and Value

- Mission
  - Ensure that safe and effective generic drugs are available for the American people.
- Vision
  - Strives to serve the public by making significant enhancements in human health through excellence and innovation in drug regulations
- Value
  - accountability, diversity, equity, excellence, integrity, and transparency

Generic Drug Approval

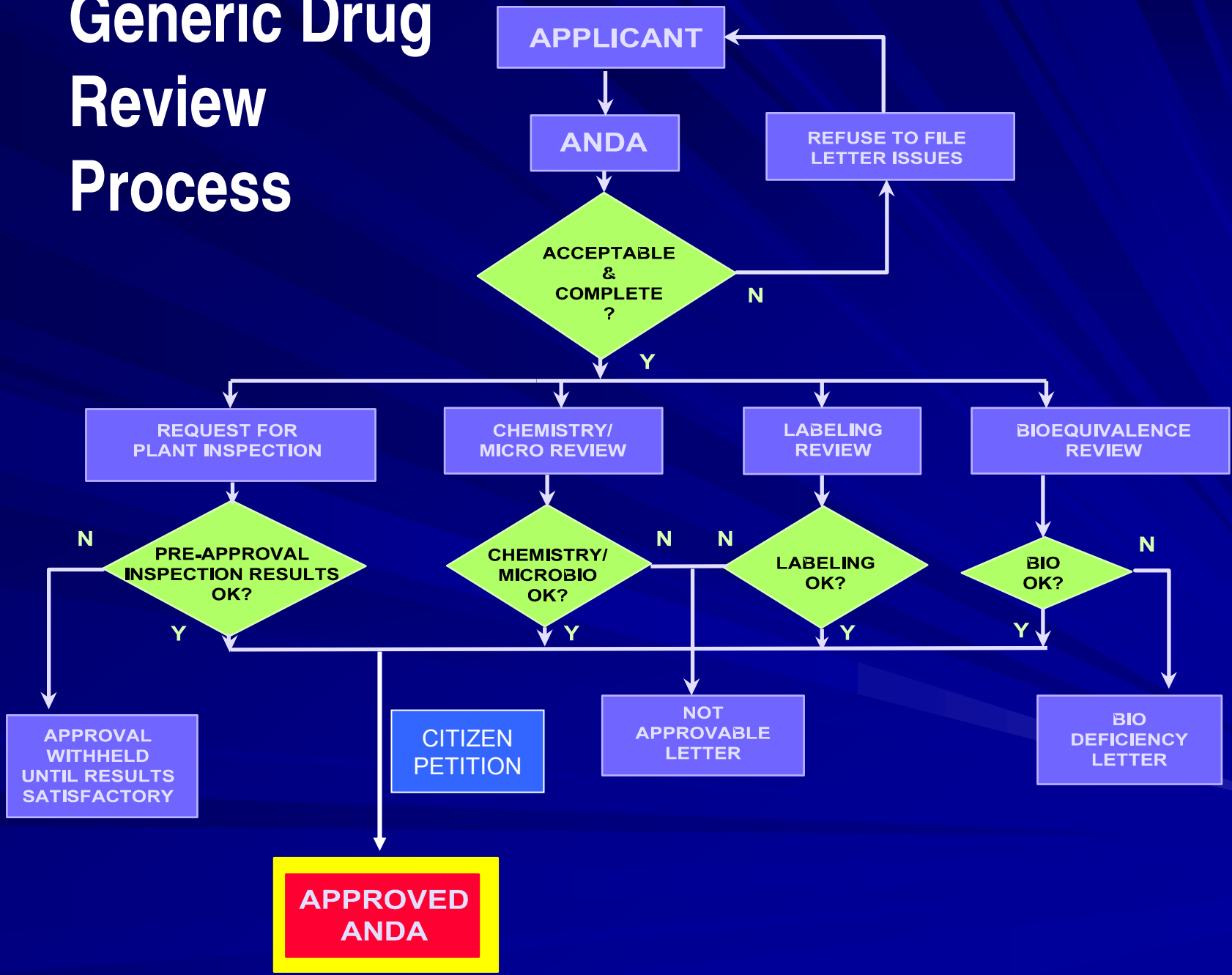
Brand Name Drug
NDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Animal Studies
7. Clinical Studies
8. Bioavailability

Generic Drug
ANDA Requirements

1. Chemistry
2. Manufacturing
3. Controls
4. Labeling
5. Testing
6. Bioequivalence

Generic Drug Review Process



What is Quality by Design?

- ICH Q8®
  - The pharmaceutical Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management
- Quality by Design includes defining of target product profile, designing product and process, identifying critical attributes (design space), and controlling manufacturing process

Quality by Design

FDA's Pharmaceutical cGMP for the 21st Century QbD Initiative

Generic Sponsor: Implementing QbD in development and manufacturing Development of Question -based Review

FDA OGD: Developed a Question-based Review System that assesses sponsor's QbD ANDAs

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
  - Comprehensively assess critical formulation and manufacturing process variables
  - Set regulatory specifications relevant to quality
  - Determine the level of risk associated with the manufacture and design of the product

QbR Principles

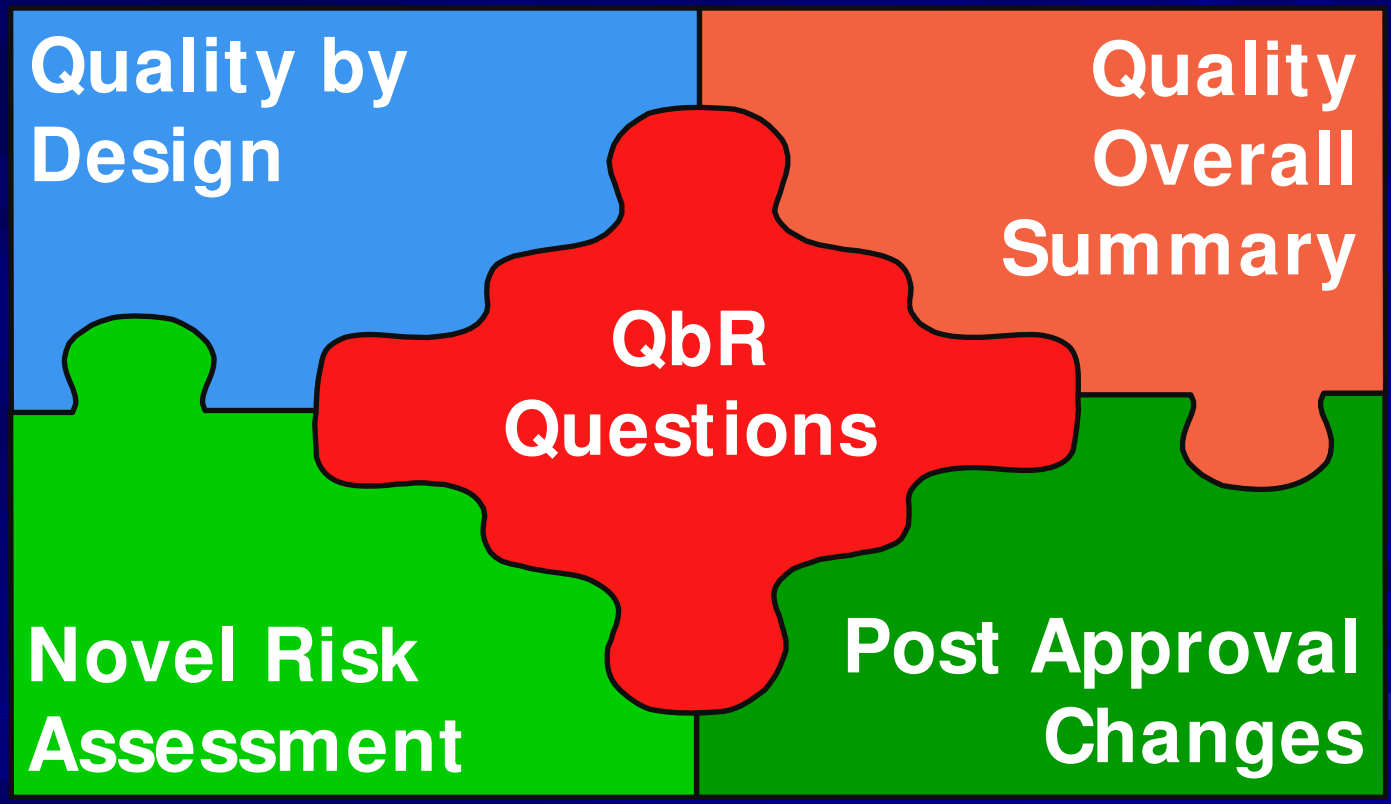
- Quality built in by design, development, and manufacture and confirmed by testing
- Risk-based approach to maximize economy of time, effort, and resources
- Preserve the best practices of current review system and organization
- Best available science and wide consultation to ensure high quality questions

Questions Come First

Say What You Do and Do What You Say

- Questions guide reviewers
  - Prepare a consistent and comprehensive evaluation of the ANDA
  - Assess critical formulation & manufacturing variables
- Questions guide industry
  - Recognize issues OGD generally considers critical
  - Direct industry toward QbD
- Questions inform readers of the review
  - How QbD was used in the ANDA
  - Provide the basis for a risk assessment

Question-based Review System



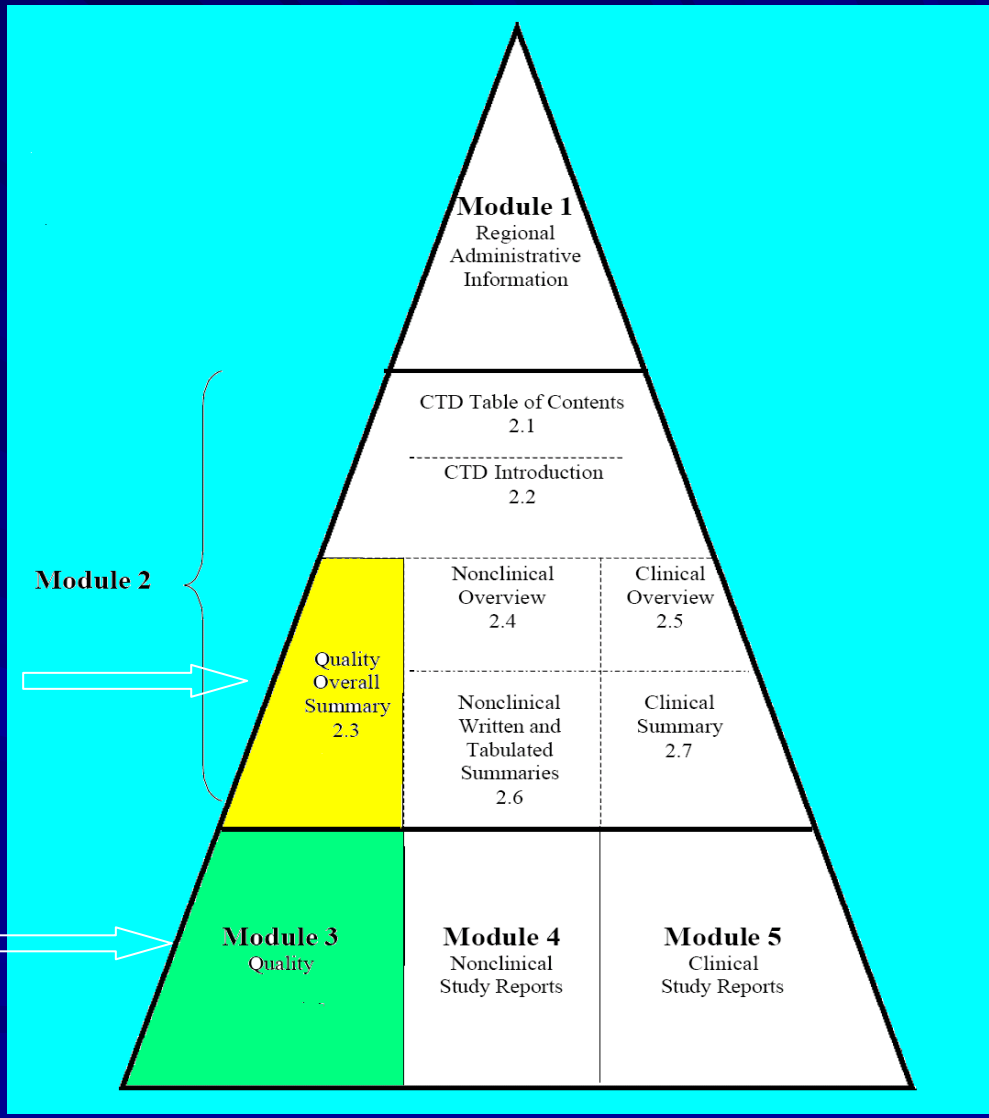
ANDAs under QbR

- Encouraging all ANDAs be submitted in the CTD format and preferably electronic CTD to support Question-based Review
  - The 1999 and 2002 Guidances for Industry; Organization of an ANDA have been removed from the Regulatory Guidance page
  - The ANDA Checklist for Completeness and Acceptability of an Application for Filing can be found on the OGD web page (4/19/2006) http://www.fda.gov/cder/ogd/

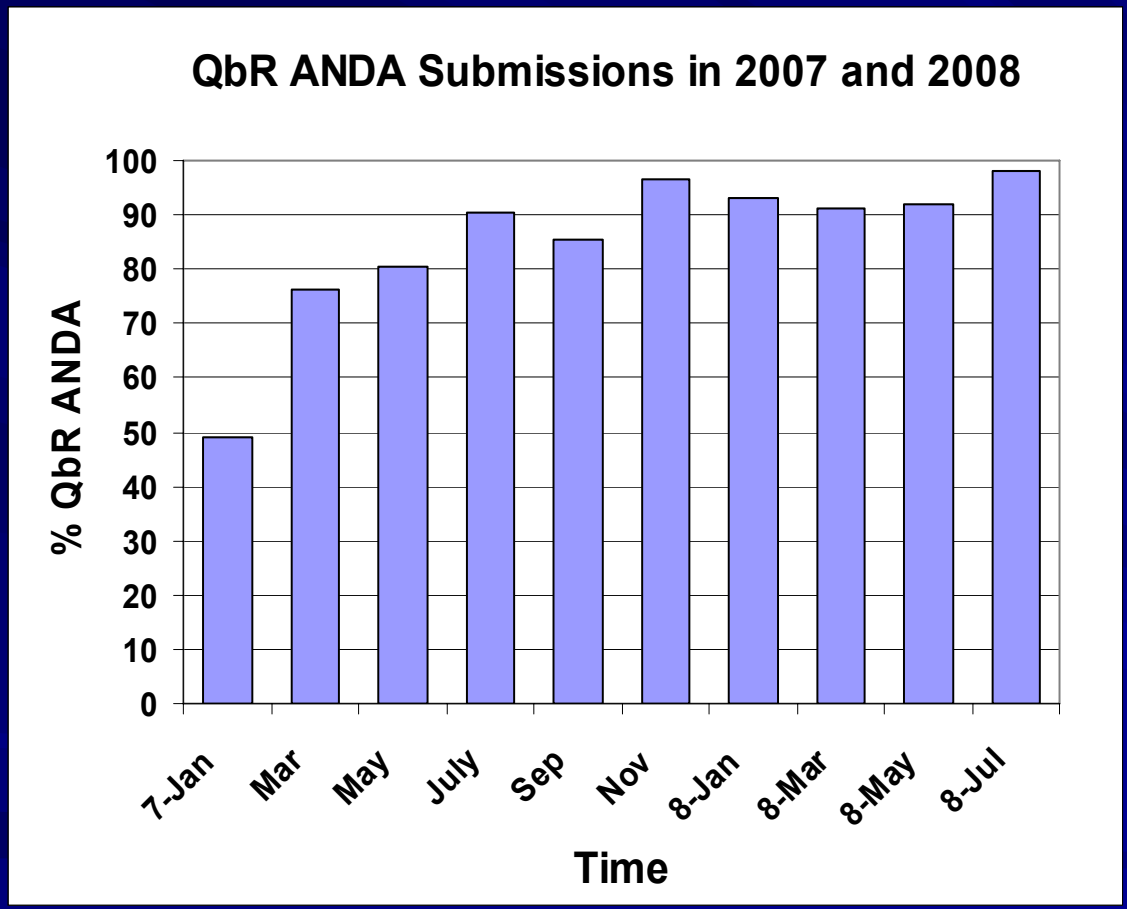
Diagram of the ICH Common Technical Document

QOS
Summary of Critical CMC Elements

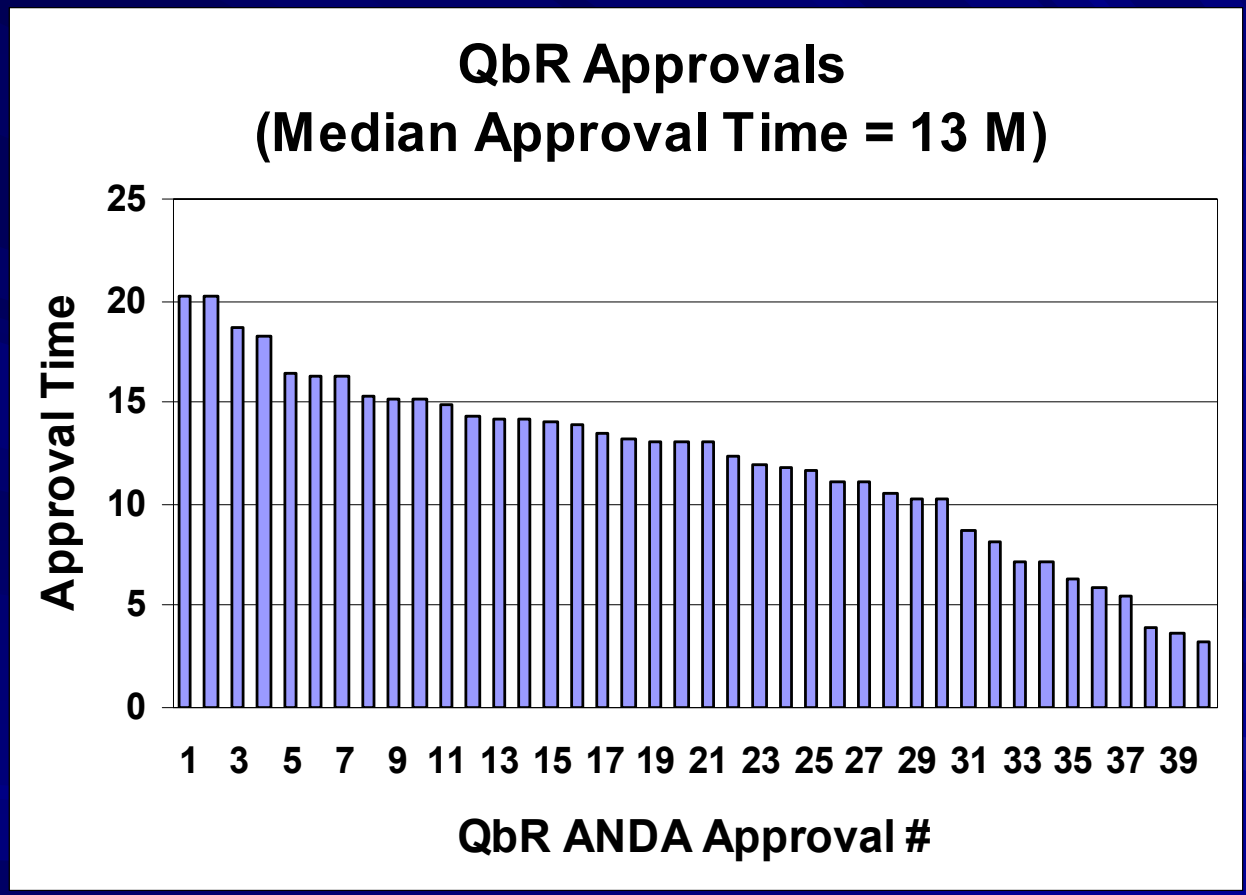
Body of Data
Detailed CMC Submission Package



QbR ANDA Submission



First 40 QbR Approvals



First 40 QbR approvals; not necessary suggesting that QbR reduce review time

QbD Questions Under QbR

- Define target product quality profile
  - What attributes should the drug product possess?
- Design and develop product and manufacturing process to meet target product quality profile
  - How was the product designed to have these attributes?
  - Were alternative formulations or mechanisms investigated?
  - How were the excipients and their grades selected?
  - How was the final formulation optimized?

QbD Questions Under QbR (Continued)

- Design and develop product and manufacturing process to meet target product quality profile
  - What are the unit operations in the drug product manufacturing process?
  - Why was the manufacturing process selected?
  - How are the unit operations related to the drug product quality?

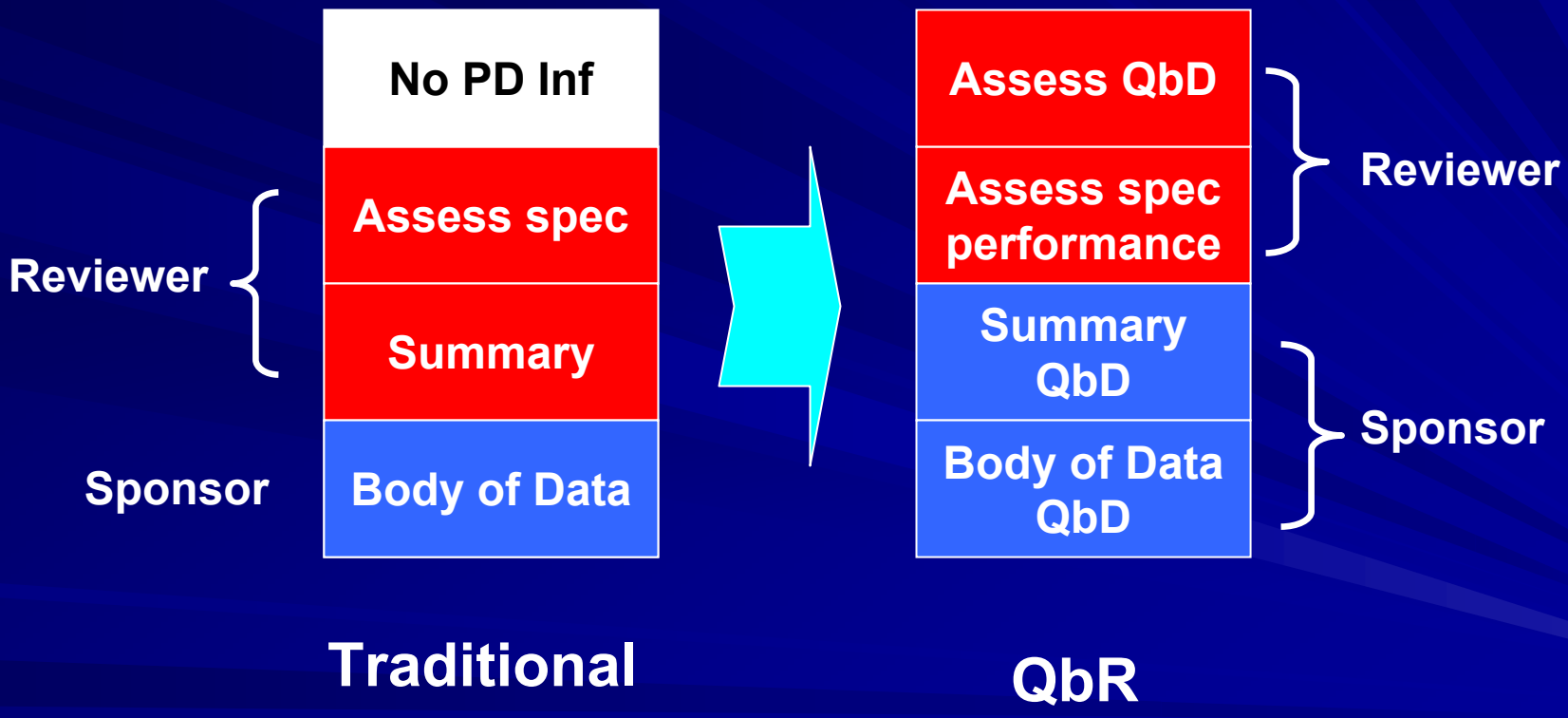
QbD Questions Under QbR (Continued)

- Identify and control critical raw material attributes, process parameters, and sources of variability
  - Which properties or physicochemical characteristics of the drug substance affect drug product development, manufacture, or performance?
  - What evidence supports compatibility between the excipients and the drug substance?
  - How were the critical process parameters identified, monitored, and controlled?

QbD Questions Under QbR (Continued)

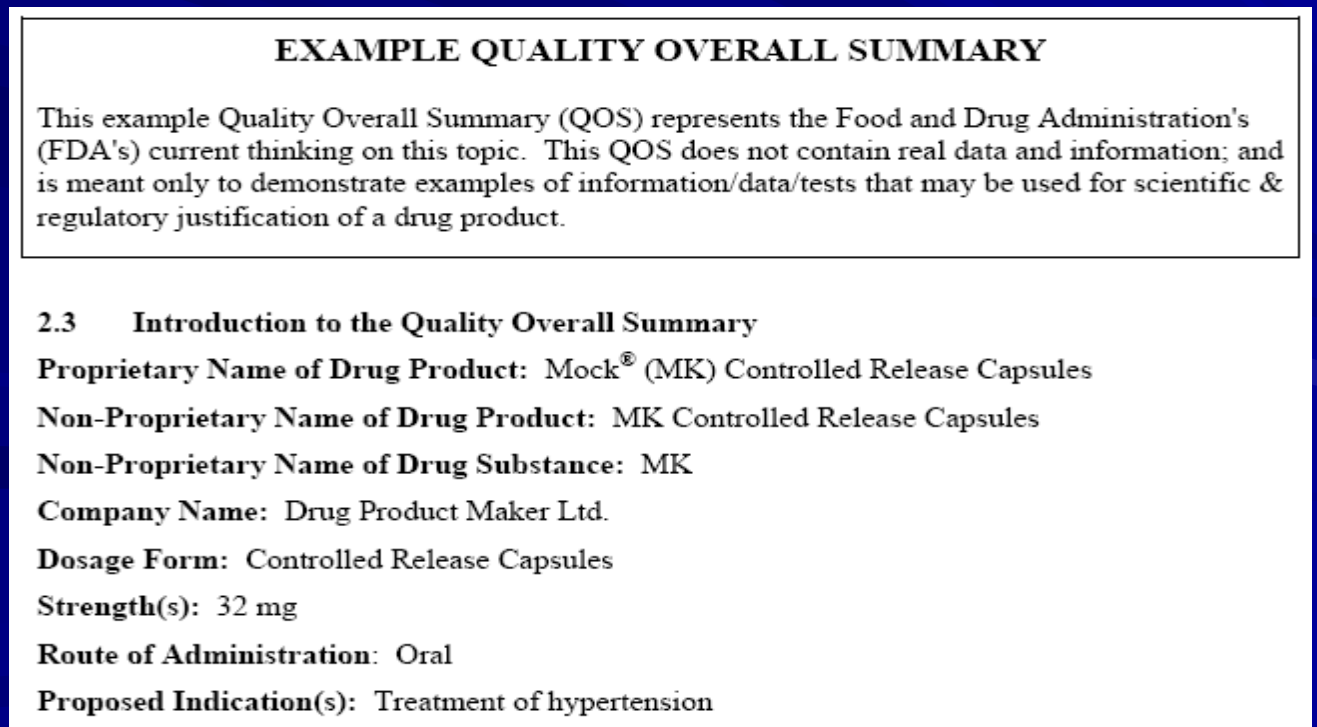
- The process is monitored and adapted to produce consistent quality over time
  - What are the in-process tests and/or controls that ensure each step is successful?
  - What is the scale-up experience with the unit operations in this process?
  - In the proposed scale up plan what operating parameters will be adjusted to ensure the product meets all in-process controls and final product specifications?
  - What evidence supports the plan to scale up the process to commercial scale?

Traditional CMC Review to QbR Assessment



OGD Model QOS

- Model QOS for ER Product (1/2006)
  - http: //www.fda.gov/cder/ogd/OGD_Model_Quality_Overall_Summary.pdf
- Model QOS for IR Product (3/2006)
  - http: //www.fda.gov/cder/ogd/OGD_Model_QOS_IR_Product.pdf



EXAMPLE QUALITY OVERALL SUMMARY

This example Quality Overall Summary (QOS) represents the Food and Drug Administration's (FDA's) current thinking on this topic. This QOS does not contain real data and information; and is meant only to demonstrate examples of information/data/tests that may be used for scientific & regulatory justification of a drug product.

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product: Mock® (MK) Controlled Release Capsules

Non-Proprietary Name of Drug Product: MK Controlled Release Capsules

Non-Proprietary Name of Drug Substance: MK

Company Name: Drug Product Maker Ltd.

Dosage Form: Controlled Release Capsules

Strength(s): 32 mg

Route of Administration: Oral

Proposed Indication(s): Treatment of hypertension

QbR Risk Assessment

- One goal of risk assessment is to allocate scarce reviewer resources to benefit the public
  - More emphasis on
    - Critical dose drugs (NTI)
    - "Complex" dosage forms/delivery systems
  - Less yet appropriate emphasis on
    - Solution products and Solid Oral IR Dosage Forms
  - Reducing supplements for minor and some moderate post-approval changes

Advantages of QbR

- Questions guide reviewers
  - Prepare a consistent and comprehensive evaluation of the ANDA
  - Assess critical formulation & manufacturing variables
- Questions guide industry
  - Recognize issues OGD generally considers critical
  - Direct industry toward QbD
- Questions inform readers of the review
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QbR Question Revision 2009

- External committee of FDA scientists to review
  - QbR questions
  - sponsors answers to the QbR questions
  - use of the QbR questions in ANDA review
- OGD WG to recommend QbR questions revision to
  - encourage firms to incorporate QbD in their ANDA submissions
  - enable better evaluation of QbD by OGD reviewers
- Public comment process before question revision

Citizen's Petitions

- 21 CFR 10.30 defines content and format of petition
- Request by individual for Fed Government to take an action articulated in the petition
- FDAAA requires FDA to respond within 6 months.
- Publicly available at 'Dockets'
  - www.regulations.gov

FDA Application Integrity Policy

- The policy focuses on the integrity of data and information in applications submitted for FDA's review and approval
- Fraud, untrue statements of material facts, bribery, and illegal gratuities
- FDA's actions
  - Refuse to approve the application (in the case of a pending application)
  - Proceed to withdraw approval (in the case of an approved application)
  - Seek recalls of marketed products etc.
  - Others

Summary

- FDA OGD's generic drug review is based on sound science and regulations
- Product design, regulatory review, quality standards, and cGMP contribute to the high quality of generic drugs
- QbR is a new quality assessment system that focuses on critical pharmaceutical quality attributes. It is transforming the ANDA CMC review into a modern, science- and risk-based pharmaceutical quality assessment system