



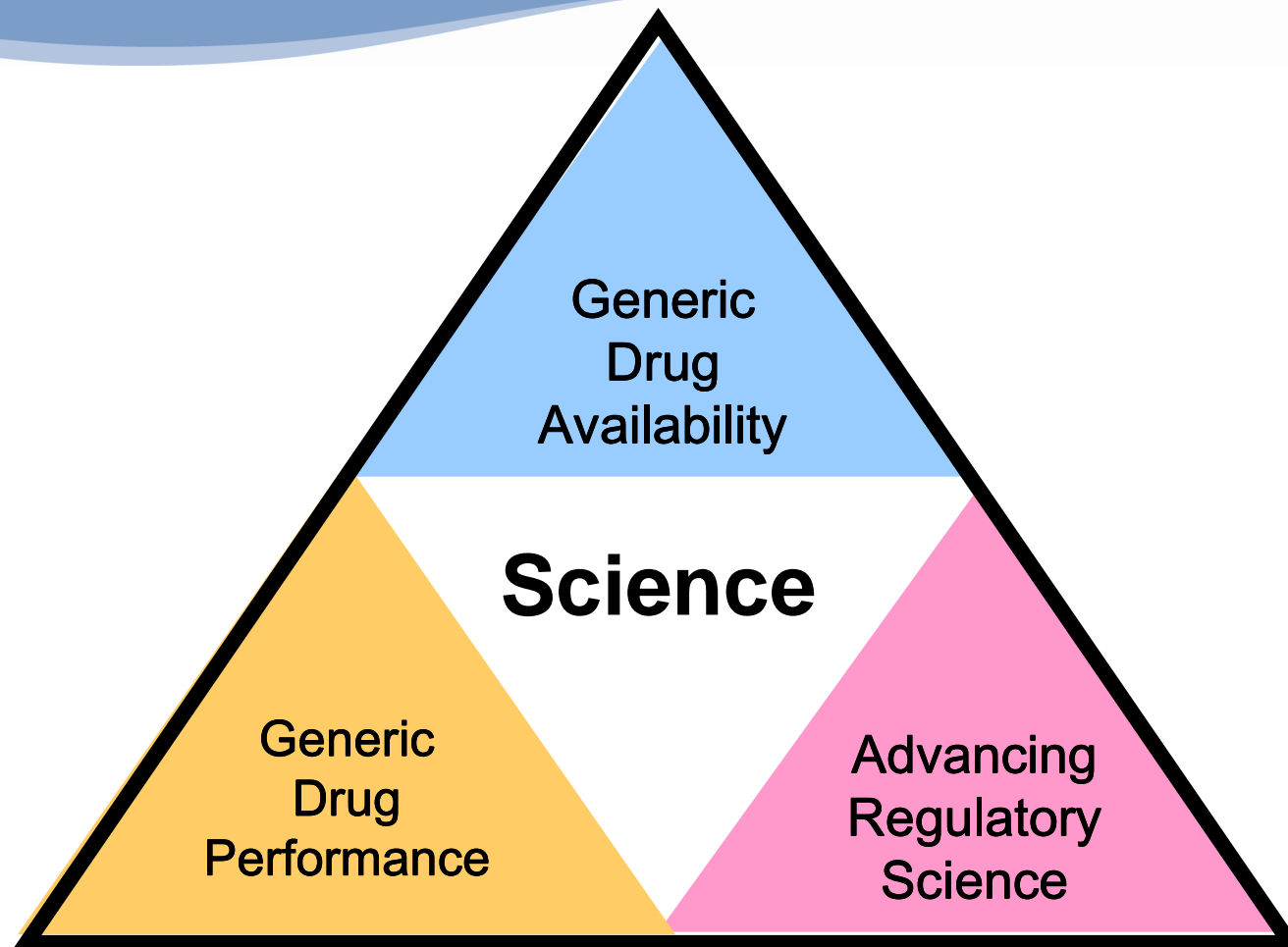
Question-based Review and Updates from the Office of Generic Drugs

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NIPTE Research Conference: Critical Path Research for
Pharmaceutical Process Scale-Up and Stability

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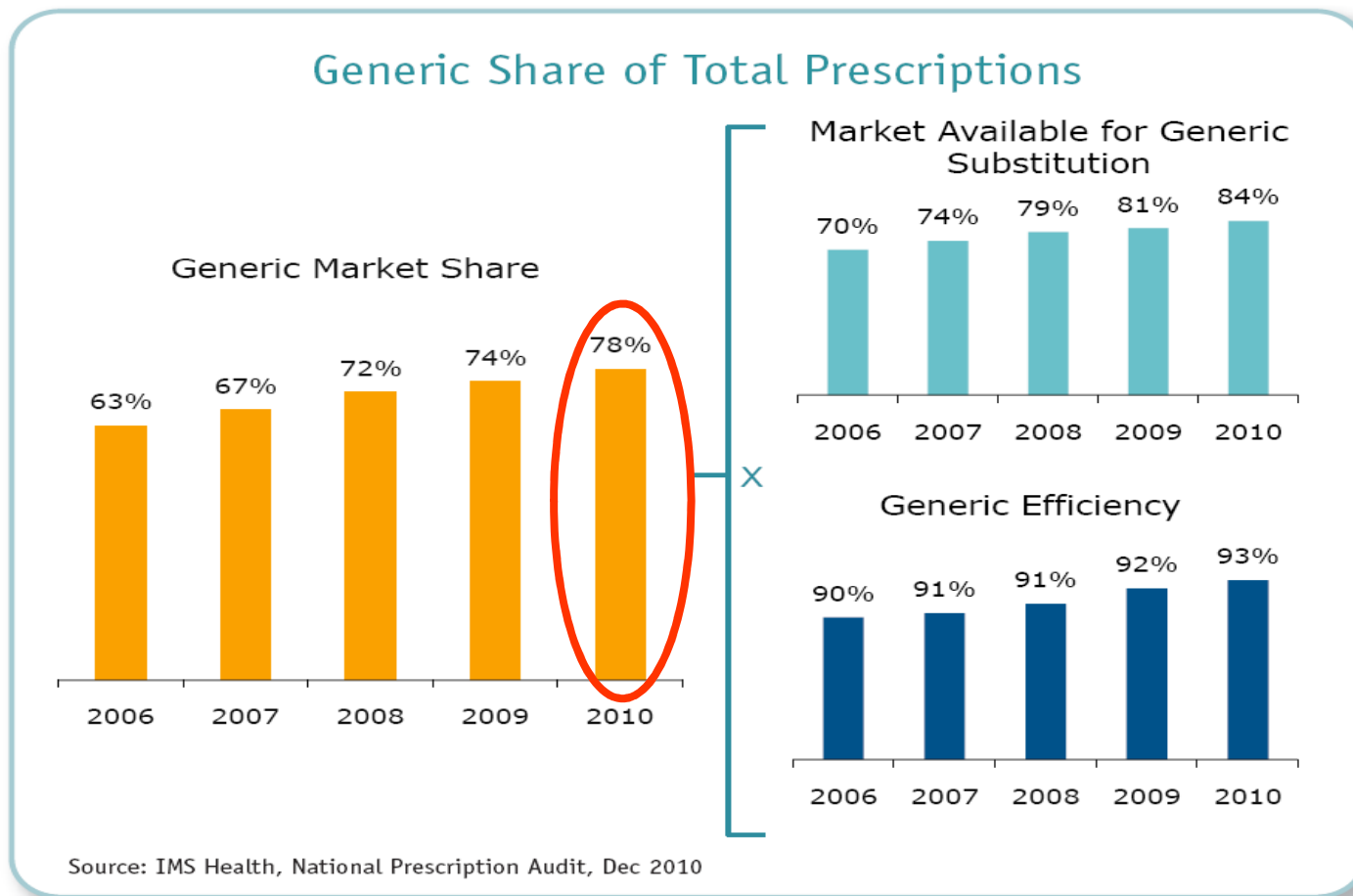
*Opinions expressed in this presentation are those of the speaker
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The foundation of generic drug availability is the science that assures equivalent performance₂



Importance of Generic Drug Availability





Importance of Generic Drug Product Availability

- Differences in product quality cannot be acceptable
- The responsibility of OGD/generic industry is to support public confidence in generic drug product quality

What is Pharmaceutical Quality?

Pharmaceutical Quality

= f (Drug substance, excipients,
manufacturing, and packaging)

- Janet Woodcock
 - Free of contamination and reproducibly delivering the therapeutic benefit promised in the label
- ICH Q8 R(2)
 - The suitability of either a drug substance or a drug product for its intended use
- Quality cannot be tested into products; quality can only be built into products





A Generic Drug is Therapeutically Equivalent to the Brand-name Drug

- Therapeutic Equivalents
 - “. . . have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”
- FDA Practice
 - Pharmaceutical Equivalence + Bioequivalence = Therapeutic Equivalence
 - Clinical trials not required to establish safety and efficacy



Pharmaceutical Equivalence

- Same active ingredient(s)
- Same dosage form
- Same route of administration
- Identical in strength or concentration
- Meet compendial or other applicable standards of strength, **quality**, purity, and identity
- May differ in shape, release mechanisms, excipients, packaging, expiration date...

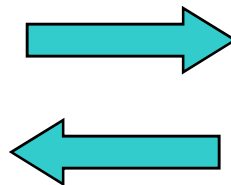


Quality by Design (QbD) and Question-based Review (QbR)

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



Quality by Design

- ICH Q8(R2)
 - 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 Tools
 - Design of Experiments (DoE)
 - Risk assessment

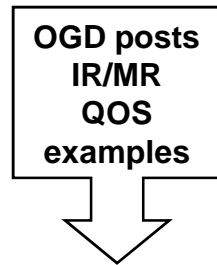


Question-based Review

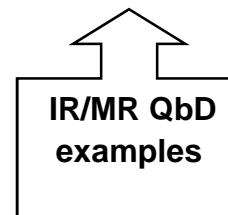
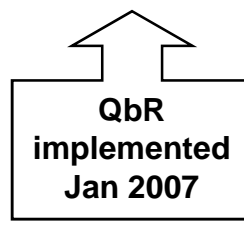
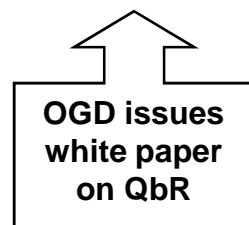
- Question-based Review (QbR) is a general framework for a science and risk-based assessment of product quality
- QbR contains the important scientific and regulatory review questions to
 - Comprehensively assess critical formulation and manufacturing process variables
 - Set regulatory specifications relevant to quality
 - Determine the level of risk associated with the manufacture and design of the product



History of QbR



- Nearly 100% ANDAs were submitted in QbR format within the first year



- Open discussion/ communication with generic industry throughout
- “We will implement together”



Reviewer Perspective of QbR

- Allows more focused Scientific Review
 - less typing and documentation time
- Guides firms to provide more pertinent and focused information → better submissions
- Facilitates a consistent review process
- Facilitates applicant's product and process understanding
- Promotes consistency in the information provided



Real Examples from QbR

- Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?
- Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?
- What evidence supports compatibility between the excipients and the drug substance?
- What is the scale up experience with unit operations in the process?
- How were the critical process parameters identified, monitored and/or controlled?
- Were alternate formulations or mechanisms investigated?



Do the differences between this formulation and the RLD present potential concerns with respect to therapeutic equivalence?

- RLD API is **surface modified nanoparticle**
- Generic uses a **conventional wet granulation method**
- Key development studies and a pivotal BE study during PD **demonstrated BE** against reference product.

Outcome: Firm directly addressed therapeutic equivalence concerns during development.



Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

- API is **BCS Class II** (low solubility)
- Generic drug product **requires wet granulation** using “solvent,” “solubilizer,” & “anti oxidant”
- API **particle size distribution is critical** to control variability (as determined during development)

Outcome: Maintain same API source to ensure future commercial batch quality and consistency.



Example before QOS - Oxygen Sensitivity for Injection Product

- API compatibility studies **not performed**
- Oxygen sensitivity **not assessed**
- New Oxidation impurity **not acceptable**

Outcome:

- Manufacturing moved to new facility
- New submission batch required
- **Delayed approval**



What evidence supports compatibility between the excipients and the drug substance?

Drug Substance compatibility was studied vs each excipient under the following conditions:

- 60°C/80% RH closed container for 15 days
- 50°C/80% RH closed container for 15 days
- 40°C/75% RH open & closed container for 1 month

Outcome: Adequate shelf life impurity profile.



Other Relevant QbR Benefits from ANDAs seen:

What is the scale up experience with unit operations in the process?

- Enteric Coated Bead Capsules: Control of pellet particle size pre and post coating

How were the critical process parameters identified, monitored and/or controlled?

- BCS Class 2 ER Tablet: Drug release properties for core and coated tablet

Were alternate formulations or mechanisms investigated?

- Low Dose Tablet: Impact of wet vs. dry, fluid bed vs. tray drying, compatibility, BUA

OPS View on Modern Manufacturing Science

- Moving toward a common view on QbD
- OPS MaPP 5016.1: “Applying ICH Q8(R2), Q9, and Q10 Principles to CMC Review”
- Focusing on better understanding through QbD concepts to reduce postmarketing issues
- QbD examples for the generic industry and FDA
 - Industry’s contribution



Helen Winkle, OPS Director, CDER, FDA



QbD Examples

- Intended to illustrate the types of development studies ANDA applicants may use as they implement QbD
- Provide a concrete illustration of the QbD principles from ICH Q8(R2)
 - Both IR and MR illustrate QbD principles
- Development of a real product may differ from the examples
- Number of experiments may depend on the experience of the applicant
 - This should be explained in the submission

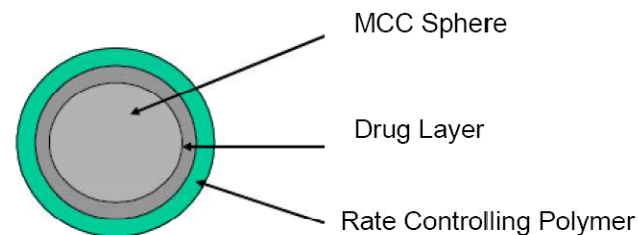
QbD IR Example

- IR tablet
 - Low solubility drug substance: Acetripitan
 - Manufactured by roller compaction
 - Uses common excipients in similar amounts to the RLD

Ingredient	Function	Weight/tablet (mg)	% (w/w)
Acetripitan, USP	Active	20.00	10
Intragranular Excipients			
Lactose Monohydrate, NF	Filler	81.5	40.75
Microcrystalline Cellulose, NF	Filler	81.5	40.75
Croscarmellose Sodium, NF	Disintegrant	6	3
Talc, NF	Glidant/Lubricant	5	2.5
Extragranular Excipients			
Magnesium Stearate, NF	Lubricant	1	0.5
Talc, NF	Glidant/Lubricant	5	2.5
Total Weight		200.0	100

QbR MR Example

- MR Tablet with IR and ER components
 - High solubility drug substance: Z
 - Biphasic release to achieve particular clinical profile
 - ER beads coated with release controlling polymer



- IR granules and ER beads compressed into a tablet
- Discussion of scale up issues



Communication

- Meetings with the Generic Industry/GPhA
 - 3 QbD Workshops – June 2009, May 2010, May 2011
 - 4 QbD Roundtable Discussions – Jun 2009, Oct 2009, Feb 2011, Apr 2011
- Prior knowledge, risk analysis



Publications

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OGD QbR and QbD: Progress

- ANDAs are being submitted in QbR format. Receiving applications containing QbD elements, meeting requests by applicants for further clarification.
- FDA Office of Generic Drugs has developed IR and MR QbD examples. To be finalized shortly.
- Upon finalizing examples, FDA Office of Generic Drugs will revise QbR questions to fully incorporate QbD elements. Further discussion is expected in 2011 and 2012.
- We expect that the revised QbR review system and QbD will be fully implemented by January 2013.



Questions/Comments?

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