Regulatory Assessment of Pharmaceutical Quality for Generic Drugs

Lawrence X. Yu, Ph.D.
Director for Science
Office of Generic Drugs, OPS, CDER
Food and Drug Administration

Presentation Outline

- **Question-based CMC Review**
  - **What is Question-based Review**
  - **Why Question-based Review**
  - **Quality by Design**
  - **Quality Overall Summary**
  - **ANDA**
  - **Risk Assessment**

Question-based Review

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

Questions to Whom?

- **CMC Reviewer**
  - **Questions guide reviewers to provide a consistent and comprehensive assessment of the application**
- **Industry**
  - **Questions also guide the industry to prepare Quality Overall Summary**

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**

Question-based Review Timeline

2004	FDA's cGMP Initiative and Initiation of QbR
1/2005	QbR Questions drafted
2/2005	GPhA Technical Advisory Committee Meeting
4/2005	PQRI and FDA Specification Workshop
6/2005	OGD GPhA Technical Advisory Committee Joint Meeting
6/2005	GPhA Technical Advisory Committee Meeting
8/2005	OGD QbR White Paper
10/2005	AAPS Quality Workshop
10/2005	OGD GPhA Technical Advisory Committee Joint Meeting
10/2005	GPhA Fall Technical Workshop
1/2006	ANDA Submission Checklist
1/2006	Example Quality Overall Summary
2/2006	GPhA Technical Advisory Committee Meeting
3/2006	OGD CMC Review Format and Example
5/2006	GPhA QbR Training

Question-Based Review for CMC Evaluations of ANDAs

The Office of Generic Drugs (OGD) is developing a question-based review (QbR) for the Chemistry, Manufacturing, and Controls (CMC) evaluation of an Abbreviated New Drug Application (ANDA) that is focused on critical pharmaceutical quality attributes. The QbR initiative began in early 2005 with the development of a revised review template and is approaching the early implementation phase as we gain feedback through wide internal and external discussions.

The QbR will transform the CMC review into a modern, science and risk-based pharmaceutical quality assessment that incorporates and implements the concepts and principles of the FDA's *Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach* and *Process Analytical Technology* initiatives

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August, 2005

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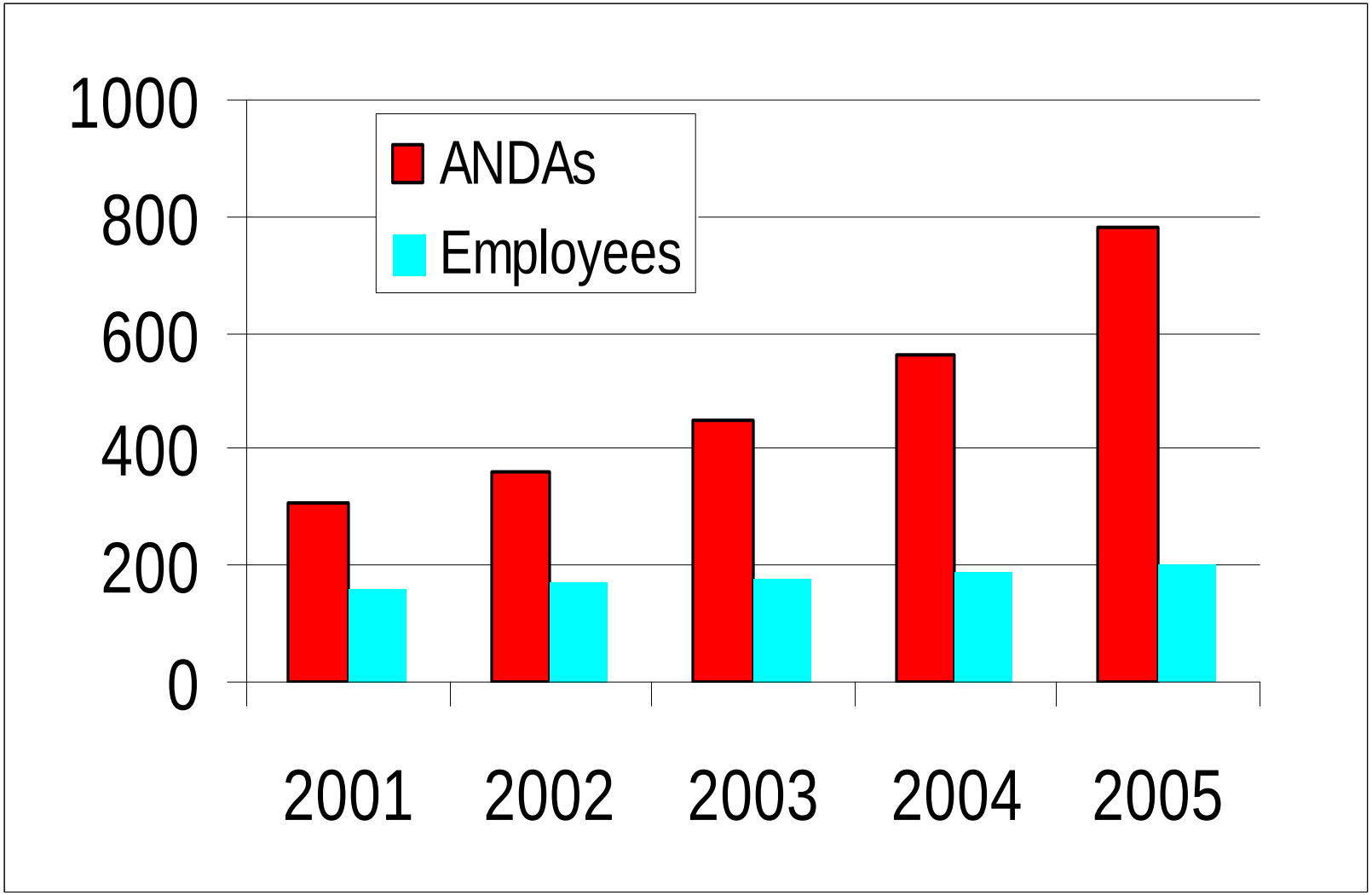
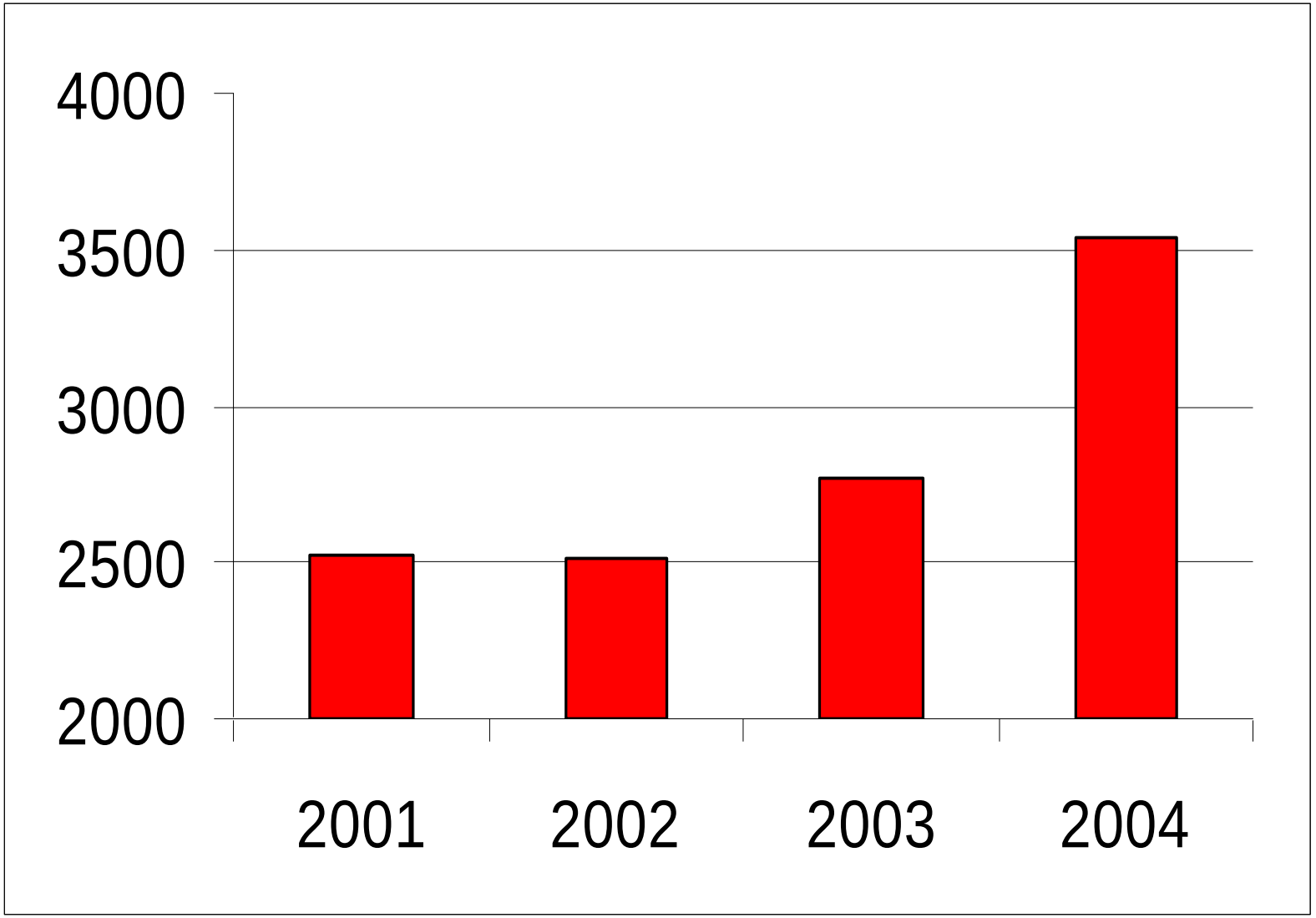
Receipts of ANDAs



Receipts of Supplements (ANDAs)



The Washington Post

Saturday, February 4, 2006

Generic Drugs Hit Backlog At FDA

No Plans to Expand Review Capabilities

By Marc Kaufman
Washington Post Staff Writer

“ …the Food and Drug Administration has a backlog of more than 800 applications to bring new generic products to the market - an all-time high.”

“Rep. Henry A. Waxman (D-Calif.), ‘This is the time for the FDA to be ramping up its generic reviews, not to be falling so badly behind.’"

cGMP Initiative "Desired State": Regulatory

- **Regulatory policies and procedures tailored to recognize the level of scientific knowledge …**
- **Risk based regulatory scrutiny that relates to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance …**

Current CMC Review: Issues

- **Quality by end product testing**
  - **Little or no scrutiny on**
    - **Product and process design**
    - **Process scale-up**
  - **In process testing**
- **Product specifications**
  - **Little or no mechanistic understanding**
  - **“Overly conservative and often irrelevant specifications”**

Current CMC Review: Issues

- **Does not adjust review to the level of scientific understanding**
  - **All products (simple and complex) use the same approach**
  - **All products are subject to the same post-approval supplements**
  - **The burdensome regulatory requirement of post-approval changes**

Why Question-based Review?

- **Workload**
  - **Number of applications is quickly growing**
  - **Number of reviewers is slowly growing**
  - **Each application leads to supplements**
- **Quality**
  - **cGMP initiative; Quality by design**
  - **Issues with current CMC review**

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What is Quality by Design?

- **Quality should be built into the product, and testing alone cannot be relied on to ensure product quality**
- **Pharmaceutical Quality by Design (QbD)**
  - **QbD means designing and developing formulation and manufacturing processes to ensure *predefined quality* by understanding how formulation and manufacturing process variables influence the quality of a drug product**

QbD: Industry

- **Develop scientific understanding of critical process and product attributes**
- **Design controls and testing based on the limits of scientific understanding at development stage**
- **Utilize knowledge gained over the product's lifecycle to operate in an environment of continuous improvement**

Janet Woodcock

QbD: Regulators

- **Assess scientifically product and manufacturing process design and development**
- **Evaluate and approve product quality specifications in light of established FDA standards (e.g., impurities, stability, etc.)**
- **Set and maintain product quality standards**
- **Evaluate post-approval changes based on risk and science**

ICH Q8 Describes Quality by Design

- **Introduced in ICH Q8**
  - **Section 3.P.2**
- **Product Development Report explains**
  - **how drug substance properties and formulation variables affect the performance of the drug product**
  - **how the sponsor identifies the critical manufacturing steps, determines operating parameters, selects in-process tests to control the process, and scales up the manufacturing process**

Two Parts of Pharmaceutical Development for Submission

- **Product design**
  - **All products**
- **Process design**
  - **Complex products only**
  - **Optional for solution, IR tablet, and IR capsule**

Product Design

- ***QbR: "Which properties or physicochemical characteristics of the drug substance affect drug product development, manufacture, or performance?"***
- **GPhA: "Information available to the applicant regarding the API is frequently restricted to the open section of a DMF. As such, information around physicochemical characterization, including polymorphs, pH, solubility, etc., can be limited unless these studies are performed by the applicant. Please comment on whether information contained only in the confidential portion of the DMF must be provided in the QOS through additional testing by the applicant, or is reference to the DMF is acceptable."**
- **OGD: Reference to the DMF is NOT acceptable**

Product Design (continued)

- ***QbR: "What evidence supports compatibility between the excipients and the drug substance?"***
- **GPhA: "In some cases, it is understood why excipient studies may be beneficial as part of the drug development program. However, in many cases, historical experience with excipients provides valuable insight into the behavior of excipients in combination with active ingredients. When firms have this historical experience, combined with stability data, is there need to routinely perform compatibility studies? This is an issue that GPhA would like to discuss further."**
- **OGD: Historical experience and theoretical analysis can be of value. If adequate, experimental data is not necessary**

Product Design (continued)

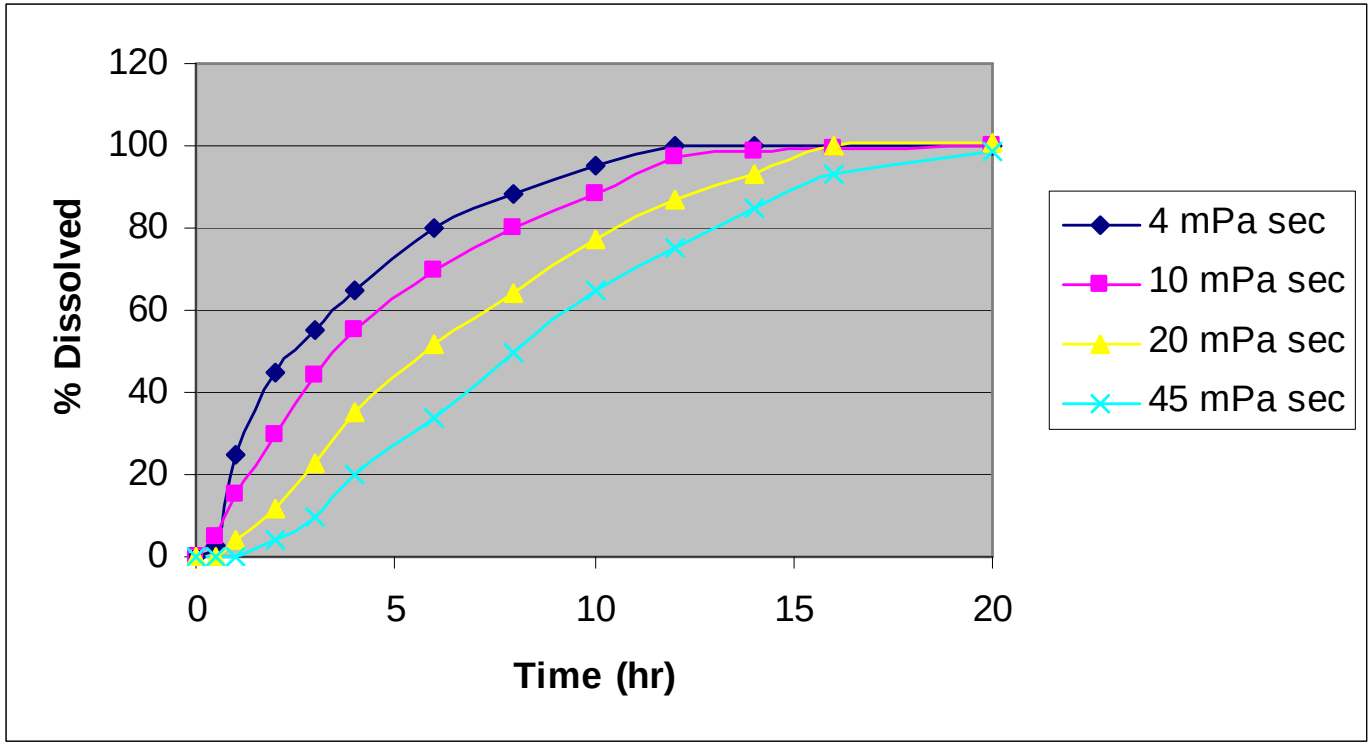
- ***QbR: "What attributes should the drug product possess?"***
- **Should include any product performance attributes**
- **OGD Example: ER Capsule; Specific**
  - **Assay**
  - **Content Uniformity**
  - **Stability**
  - **Drug release profiles**
  - **Acceptable capsule characteristics**
  - **Any others that affect the product performance**

Product Design (continued)

- ***QbR: "How was the product designed to have these attributes?"***
- **OGD Example: IR Tablet**
  - **Particle size of the drug substance in the drug product**
  - **Polymorphic form of the drug substance in the drug product**
  - **Assay of drug substance in the drug product**
  - **Content uniformity of drug substance in the drug product**
  - **Level of disintegrant in the drug product**
  - **Tablet friability and hardness**
  - **Level of degradation products**
  - **Container closure protects drug product from light**

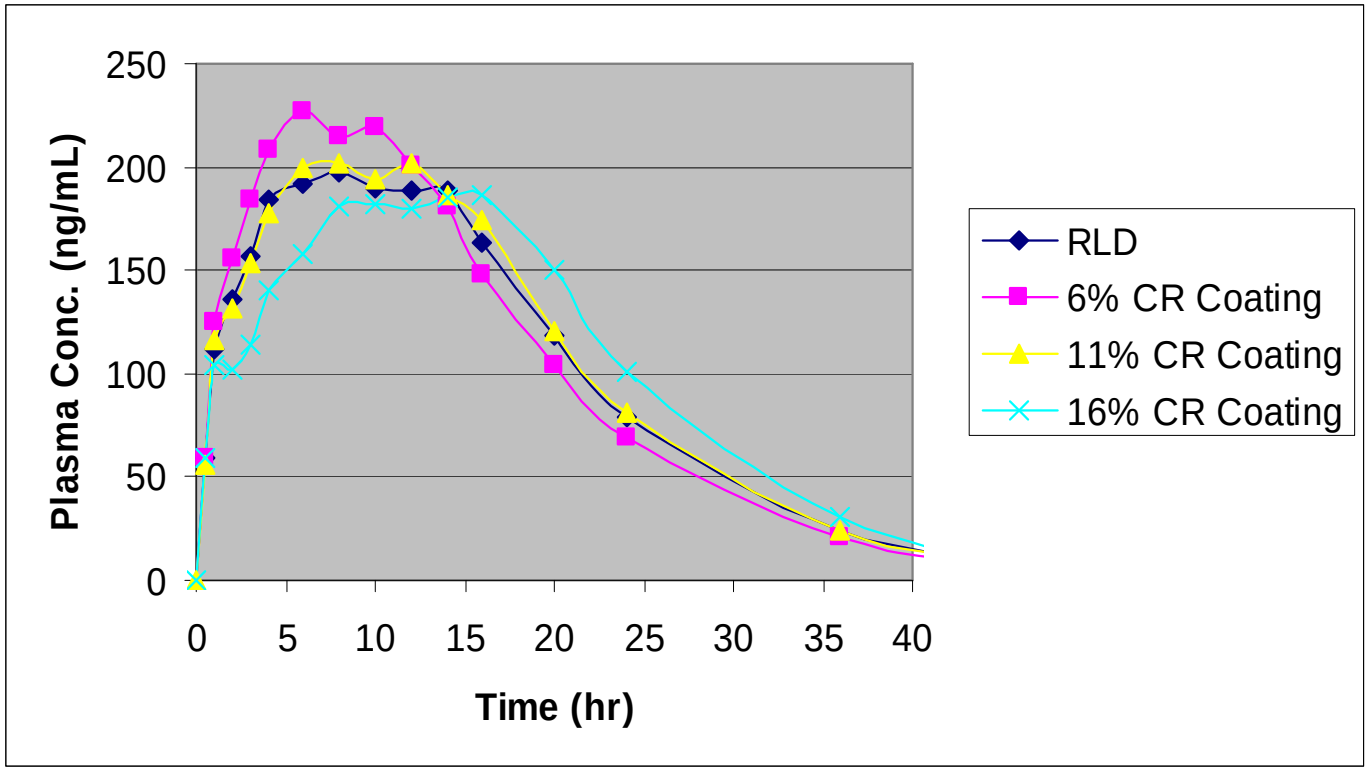
Product Design (continued)

- ***QbR: "How were the excipients and their grades selected?"***
- **OGD Example: ER Capsule; Polymer grade**



Product Design (continued)

- *QbR: "How was the final formulation optimized?"*
- **OGD Example: ER Capsule**



Formulation Design Space?

- **ICH Q8**
  - **Design Space: The established range of process parameters that has been demonstrated to provide assurance of quality. In some cases design space can also be applicable to formulation attributes.**
- **Formulation Design Space?**
  - **The established range of formulation parameters (i.e., excipient ranges) that has been demonstrated to provide assurance of quality.**

Process Design

- ***QbR:* "*Why was the manufacturing process described in 2.3.P.3 selected for this drug product?"***
- **OGD Example: ER Capsule**
- ***Coating Process*:**
  - **… The rationale for selecting this process was two fold:**
    - **The Wurster process results in highly uniform coating of particulates. In terms of process design, this is essential to ensure both content uniformity (uniform MK coating sugar spheres) and reproducible drug release (uniform CR coating layered on sugar spheres).**
    - **Prior manufacturing knowledge utilizing a Wurster coating process and similar functional CR coating mechanism is available ((IT ER Capsules (ANDA wwww)).**

Process Design (continued)

- ***QbR: "How are the manufacturing steps (unit operations) related to the drug product quality?"***
- **OGD Example: ER Capsule**

	Raw Material	Drug Layering	CR Coating	Encapsulation
Purity	**High**			
Assay/Content Uniformity		**High**		**High**
Release Profile	**High**		**High**	**High**
Stability			**High**	

Process Design (continued)

- ***QbR: "How were the critical process parameters identified, monitored, and/or controlled?"***
- **OGD Example: ER Capsule**

D.O.E. CR Process Variables Studied

Process Variable	Minimum	Maximum
Product Bed Temperature	**40°C**	**70°C**
Atomizing Air Pressure	**1 bar**	**5 bar**
Fluidization Air Volume	**70 m^3/h**	**150 m^3/h**
Spray Rate	**10 mL/min**	**70 mL/min**
CR Coat Solids Content	**10%**	**30%**
Droplet Size	**5 µm**	**70 µ m**

Process Design (continued)

- ***QbR: "What is the scale-up experience with the unit operations in this process?"***
- **OGD Example: ER Capsule**

Process Parameters			Rationale
Fluidizing air volume (m^3/hr)	**90-110**	**540-660**	**Linear scale-up based upon distribution-plate area ratio^2**
Inlet air temperature (^{o}C)	**55-62**	**55-62**	**Scale-independent variable**
Product bed temperature (^{o}C)	**37- 43**	**37-43**	**Scale-independent variable**
Spray rate (mL/min)	**25-30**	**150-180**	**Linear scale-up based upon distribution-plate area ratio**
Atomizing air pressure (bar)	**1.5**	**2.5**	**Due to the higher spray rate, the nozzle atomizing air pressure was increased to maintain the same median spray droplet size**
Coating Efficiency	**99%**	**99%**	**N/A**

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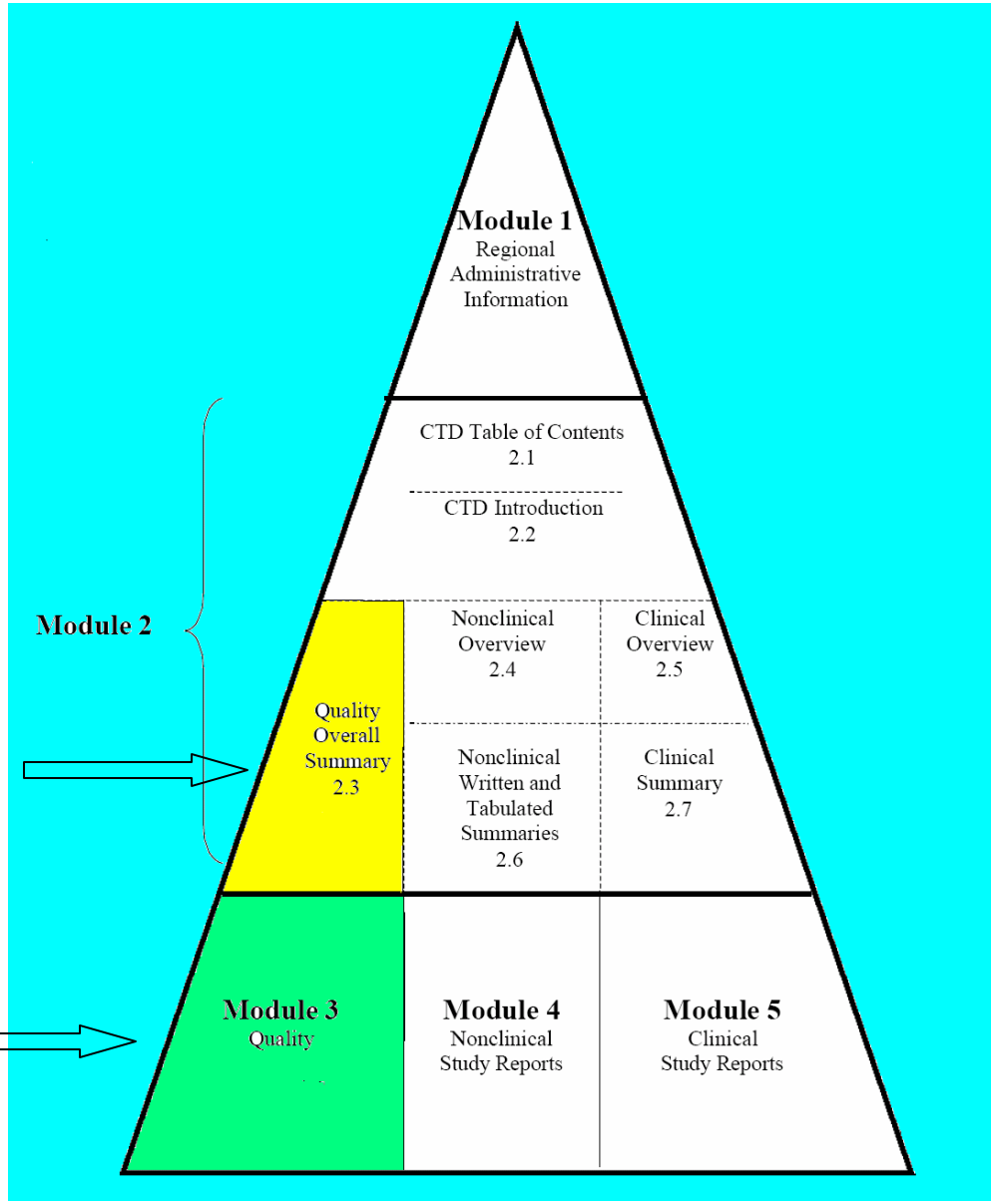
Diagram of the ICH Common Technical Document

QOS
Summary of Critical CMC Elements

Body of Data
Detailed CMC Submission Package



CTD Applications

Module 2: QOS

2.3.P DRUG PRODUCT
2.3.P.1 Description/Composition of the Drug Product

2.3.P.2 Pharmaceutical Development

2.3.P.3 Manufacture

2.3.P.4 Control of Excipients

2.3.P.5 Control of Drug Product

2.3.P.6 Reference Standards or Materials

2.3.P.7 Container Closure System

2.3.P.8 Stability

Module 3: Body of Data

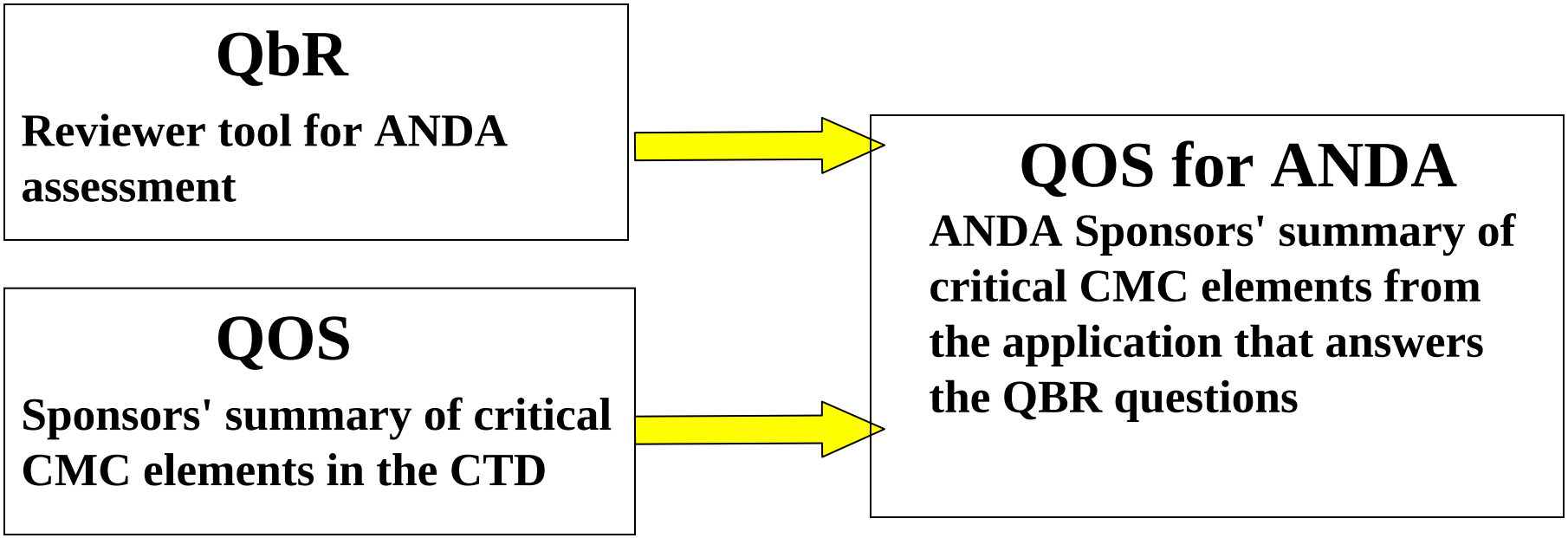
2.3.P DRUG PRODUCT
…
…
…
….

3.2.P.3 Manufacture
3.2.P.3.1 Manufacturers
3.2.P.3.2 Batch Formula
3.2.P.3.3 Description of Manufacturing Process/ Process Controls
3.2.P.3.4 Controls of Critical Steps and Intermediates
3.2.P.3.5 Process Validation and/or Evaluation
…
…
…
…
…

QOS Will Result in Efficient Question-based Review

- **One application format**
  - **Common Technical Document Format**
- **Quality Overall Summary that will**
  - **directly address the OGD's QOS questions**
  - **result in a better understanding of sponsors' rationale for decisions and therefore, less misunderstandings**
  - **reduce reviewers' time spent in fact finding and summarizing ANDA elements**

QbR-QOS for ANDAs



QbR-QOS based CMC Review

Sponsor's QOS + **Reviewer's Assessment** = **CMC Review**

No Sponsor's QOS = **?**

ICH QOS

2.3.P DRUG PRODUCT

2.3.P.1 Description/Composition of the Drug Product

2.3.P.2 Pharmaceutical Development

2.3.P.3 Manufacture

2.3.P.4 Control of Excipients

2.3.P.5 Control of Drug Product

2.3.P.6 Reference Standards or Materials

2.3.P.7 Container Closure System

2.3.P.8 Stability

QbR-QOS

2.3.P DRUG PRODUCT

…
…
…
…

2.3.P.5 Control of Drug Product

What is the drug product specification?
Does it include all the critical drug product attributes?

For each test in the specification,
is the analytical method(s) suitable for its intended use and, if necessary, validated?
What is the justification for the acceptance criterion?

Example QbR - QOS

2.3.P.5 Control of Drug Product
What is the drug product specification? Does it include all the critical drug product attributes?

Tests	Acceptance Criteria	Analytical Procedure	Results lot #P034
Description	No. 1 blue green opaque cap/yellow opaque body hard shell gelatin capsule filled. The capsule is axially printed with "MK" over "32' in white ink on both the cap and body.	Visual	Complies
Appearance	No observation of discoloration, softening, stickiness brittleness, or cracking	Visual	Complies
Identification	1. HPLC: The retention time of the major peak in the chromatogram of the assay preparation corresponds to that of the standard preparation as obtained in the assay	In-House HPLC Test Method #125b	Complies
	2. UV: Spectrum corresponds to that of corresponding preparation of the reference standard	In-House HPLC (PDA Detector) Test Method #125b	Complies
Drug Release	Time / % Dissolved 0.5 hr: Between 25-35% 4 hr: Between 40-60% 8 hr Between 65-85% 12 hr: NLT 85%	Medium: 900 mL, 0.05 M Phosphate Buffer (pH 6.8) at 37 ºC. Apparatus: 1 (basket) at 100 rpm	0.5 hr: 27-31% 4 hr: 48-53% 8 hr: 73-78% 12 hr: 90-94%
Uniformity of Dosage Units	USP <905>	In-House HPLC Test Method #125c	99.1-101.3% RSD=0.8%
Assay	95.0-105.0%	In-House HPLC Test Method #125b	101.2%
Degradation Products	Impurity A: NMT 1.5% Impurity E: NMT 1.0% Any Unknown Impurity: NMT 0.2% Total Impurities: NMT 2.5%	In-House HPLC Test Method #231b	0.8% 0.4% 0.07% 1.5%
Moisture	NMT 3.5%	Karl Fischer Titration (USP <921> Method 1a)	2.9%

QOS and CMC Deficiency

- **Should QOS be updated when sponsors address CMC deficiencies each time?**
- **OGD: Yes**

QOS GPhA Questions

- **If a question is not applicable to a specific formulation or dosage form should the question/section be deleted or unanswered?**
- **OGD: N/A with a brief explanation**

- **With regard to sterile injectables, to what extent should Sterility Assurance issues (such as filter validation) be covered in the QOS?**
- **OGD: Current QOS covers chemistry only**

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Guidance for Industry

Organization of an ANDA

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
February 1999
OGD # 1
Revision 1

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2002
Electronic Submissions

Guidance for Industry

Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services

Food and Drug Administration

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

October 2005

Electronic Submissions

ANDAs

- **ICH CTD**
  - **Module 1: Administrative Information**
  - **Module 2: Quality Overall Summary and Clinical Summary**
  - **Module 3: Quality**
  - **Module 4: Nonclinical**
  - **Module 5: Clinical (Bioequivalence)**

Generic Drug Development, Abbreviated New Drug Application (ANDA) Submissions, and Review Information

- **ANDA Checklist for Completeness and Acceptability [PDF] [Word]（1/17/2006)**
  - **…**
  - **Quality Overall Summary (QOS)**
    - **E-Submission: _____PDF (archive) ____ Word Processed e.g., MS Word**
  - **…**

Please submit your ANDAs in CTD, preferably electronic, now!

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Risk-based Approach

- **One goal of risk assessment is to allocate scarce reviewer resources to benefit the public**
  - **More emphasis on**
    - **Critical dose and drugs (NTI)**
    - **"Complex" dosage forms/delivery systems**
      - **Release mechanism; lipid based drug delivery system; parenteral controlled release products; liposomes…**
  - **Less yet appropriate emphasis on**
    - **Solution products**
    - **Solid Oral IR Dosage Forms**
    - **Eliminating supplements for many minor and most moderate and some major changes**

Manufacturing Process Assessment

- **Three-tiered assessment of manufacturing**
  - **Tier 1 applies to all dosage forms**
  - **Tier 2 applies to dosage forms that are not solutions (equivalent to current practice)**
  - **Tier 3 applies to dosage forms that are not solutions, IR tablets, or IR capsules**

Post-approval Changes

- **Draw conclusions about risk that will be useful in evaluating the need for post approval supplements**
  - **Eliminate/downgrade up to 80% of CMC supplements, and thus free up scarce resources**
- **Allow sponsors freedom to execute manufacturing processes for which they have demonstrated process understanding**
  - **Facilitating continuous CMC improvement and innovation**

Proposed Risk-based Scoring System

- **ANDA drugs:** **Risk score**

NTI Drugs	**+1**
Complex dosage form	**+1**
Insufficient or missing PD reports	**+1**
Application of poor quality	**+1**

- **Possible risk scores = 0, 1, 2, 3, or 4**
- **The review team proposes a final risk assessment score**

What post-approval waivers/ commitments are appropriate?

- **Total risk score of 1 or less**
  - **Many CBE-0 and CBE-30 changes shifted to annual report**
  - **Possible to downgrade certain PAS changes to CBE/annual report**
- **Total risk score of more than 1**
  - **No change in supplement submission and review**

Benefits of QbR

- **High product quality**
  - **Quality by design**
- **Efficient and timely review**
  - **Quality overall summary**
- **Risk based reduction of supplements**
  - **Up to 80% for ANDAs**
- **Science based specifications**
  - **Safety and efficacy, not process capability**
- **Consistency and transparency of review**

Summary

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