On-site Visit
OPS / OC / ONDQA / OGD

Yukio Hiyama, Ph.D.
Chief, Third Section, Division of Drugs
National Institute of Health Sciences
1-18-1 Kamiyohga, Setagayaku, Tokyo 158-8501

October 1 and 2, 2007

Day 1

8:00	OPS Meet and Greet	Helen Winkle Jon Clark Ted Sherwood
8:30	Transit to Office of Compliance	David Morley
9:00	Introductions and Manager Discussions	Deb Autor Joe Famulare Rick Friedman
9:30	Pre-approval Inspection	Alicia Mozzachio Doug Campbell
10:15	Break	
10:30	CGMP Conformance / Surveillance Inspection	Alicia Mozzachio Doug Campbell
11:00	Inspection Site Selection Model: Design and Operation	Gregg Claycamp PhD
11:30	Closing Remarks and Discussion	Deb Autor Joe Famulare Rick Friedman
12:00	Lunch with OC	
12:45	Transit to OGD	Rick Friedman
1:00	Generic Drug Application Review Process and Practices – Role of USP standards in review – OGD Question Based Review	Gary Buehler
2:30	Break	

2:45	Discussion / Q&A	
4:00	Adjourn	
4:30	Dinner (with Moheb and other FDA managers)	

Day 2

8:30	ONDQA Overview – NDA Review Process – CMC Pilot	Moheb Nasr / Chi-wan Chen
10:00	Seminar (Research or Regulatory Topic) Conference Room 2205	Yukio Hiyama
11:00	Q & A	
11:30	Lunch	Moheb, Chi-wan, Arzu, DDs
1:00	Division of Pre-marketing Assessment I	Blair Fraser Ramesh Sood Ali Al-Hakim
2:00	Division of Pre-marketing Assessment II	Elaine Morefield Moo-Jhong Rhee Norm Schmuff
3:00	Break	
3:15	Division of Pre-marketing Assessment III and Manufacturing Science	Rik Lostritto Ravi Harapanhalli Christine Moore
4:15	Division of Post-marketing Evaluation	Eric Duffy Jim Vidra Hasmukh Patel
5:15	Wrap-up	Moheb Nasr / Chi-wan Chen

An Overview of the Office of Generic Drugs

Timothy Ames, R.Ph., M.P.H.
Chief, Review Support Branch
Office of Generic Drugs
October 1, 2007

Office of Generic Drugs Mission Statement

To ensure through a scientific and regulatory process, that generic drugs are safe and effective for the American public.

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Did you know that generic drugs...

- Are safe and effective alternatives to brand name prescriptions
- Can help both consumers and the government reduce the cost of prescription drugs
- Generics represent 63% of the total prescriptions dispensed in the US, but only 20% of all dollars spent on prescription drugs. *
- Save approximately $53 for every prescription sold.

*Source: Generic Pharmaceutical Association, *GPhA Praises House Subcommittee for Increasing Funding for Office of Generic Drugsbout Generic Pharmaceuticals,* 7/25/07. http://www.gphaonline.org

Breakdown of FTEs – Office of Generic Drugs

■ Total	214
♦ Chemists	84
♦ Bioequivalence/Pharmacologists	32
♦ Pharmacist/Project Managers	66
♦ Medical Officers	3
♦ Math Statisticians	3*
♦ Microbiologists	8
♦ IT Specialists	2
♦ Admin/Support Staff	19

*(do not belong to OGD)

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OGD Major Responsibilities

- Review and Approve Abbreviated New Drug Applications(ANDAs)/Supplements
- Provide Regulatory/Technical Guidance to Industry (Controlled Documents)
- Address Scientific Issues concerning Generic Drug Products (Citizens' Petitions, etc.)
- Develop/Improve Review Processes for ANDAs
- Educate & Train a diverse staff in latest Scientific, Regulatory, and Review technologies
- Educate American Public about FDA approved Generic Drug Products

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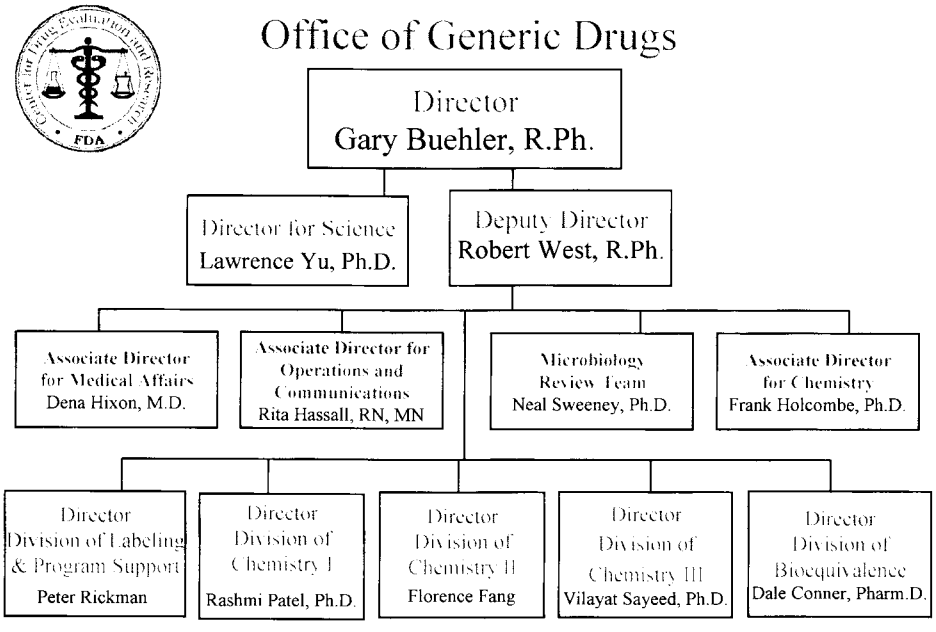
Office of Generic Drugs



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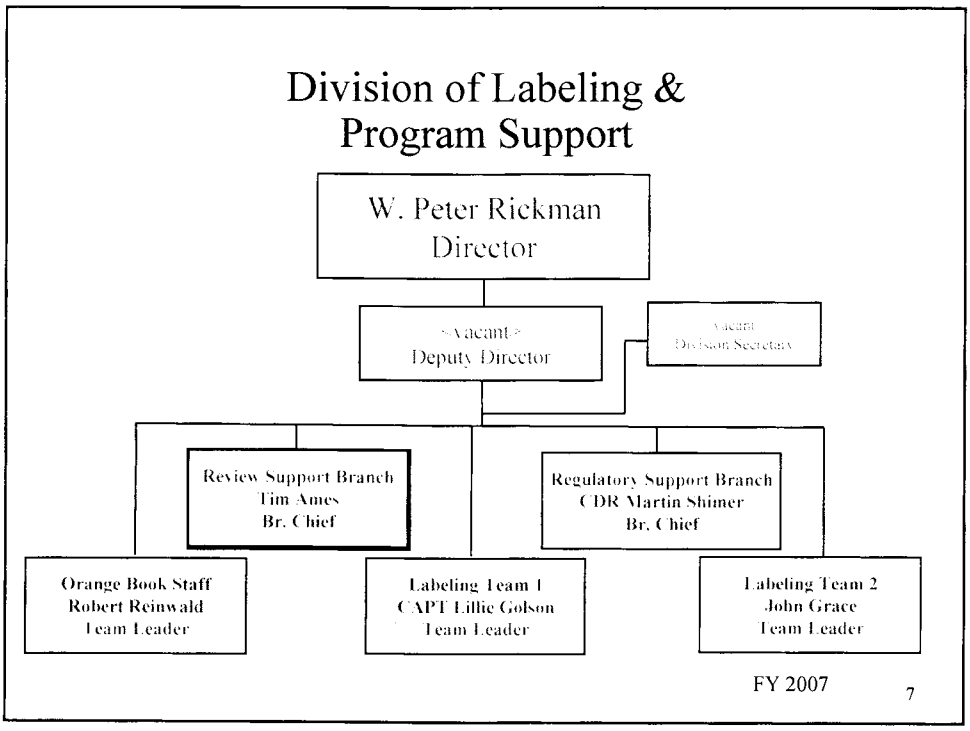
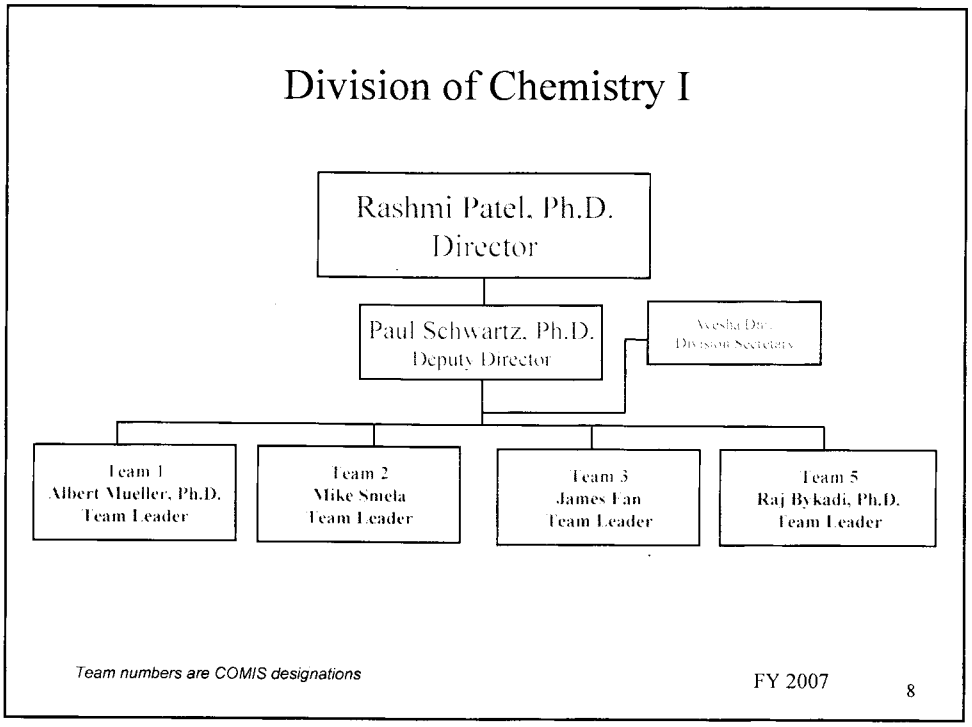
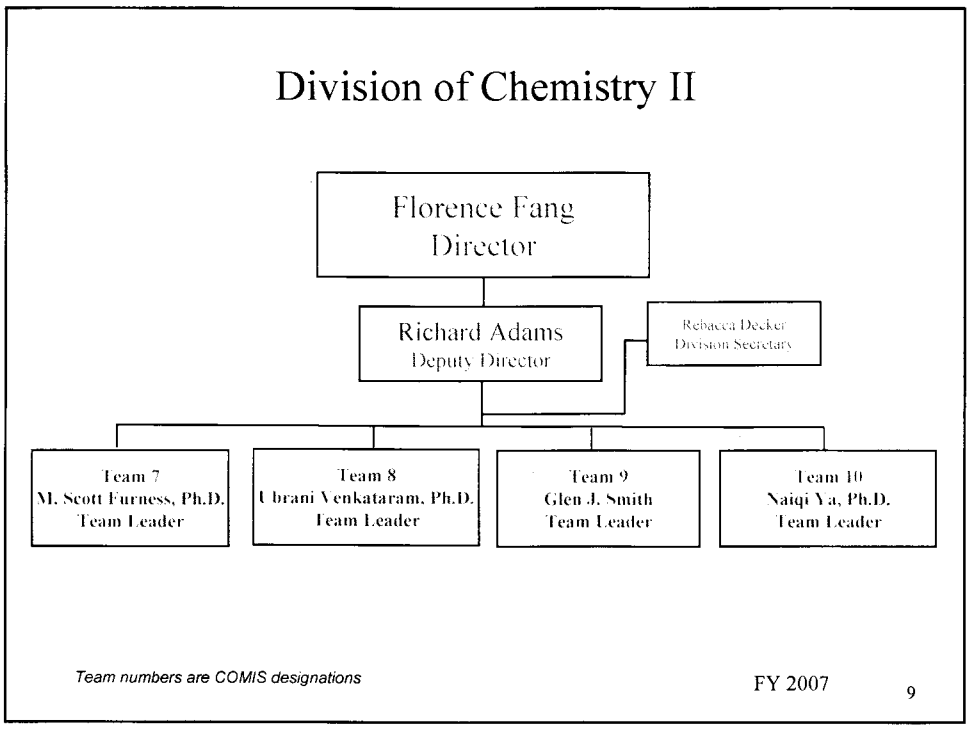
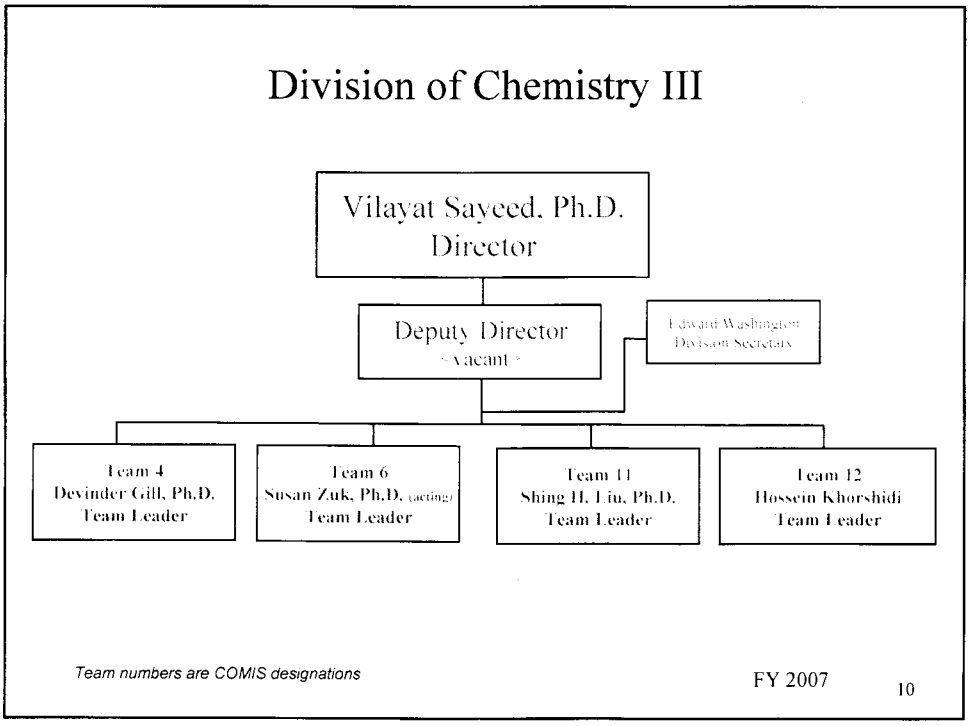
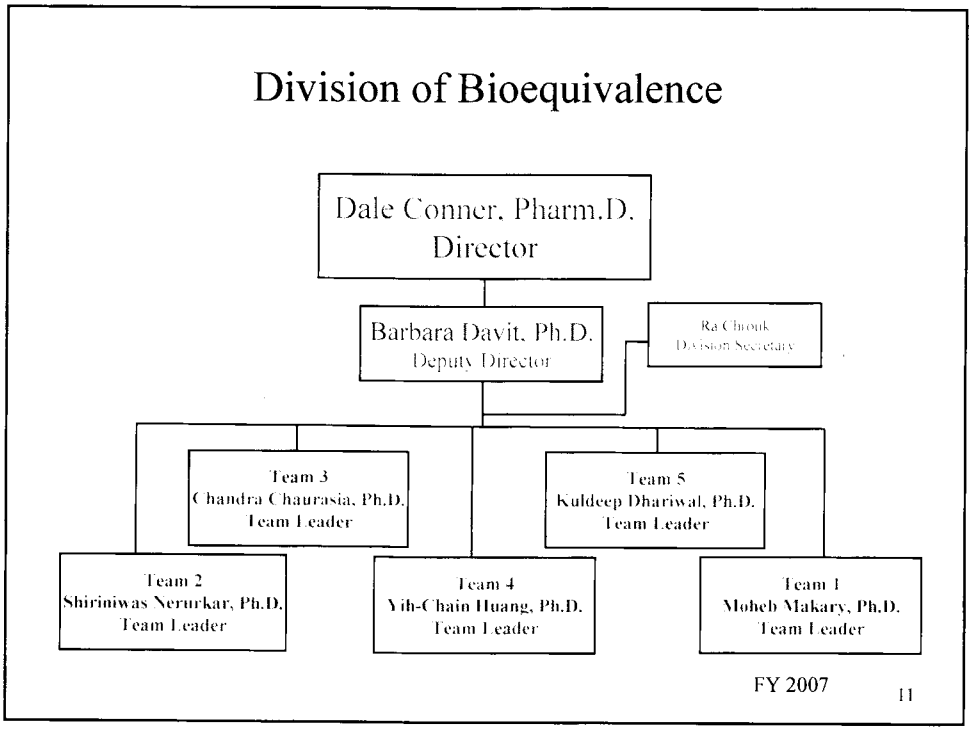
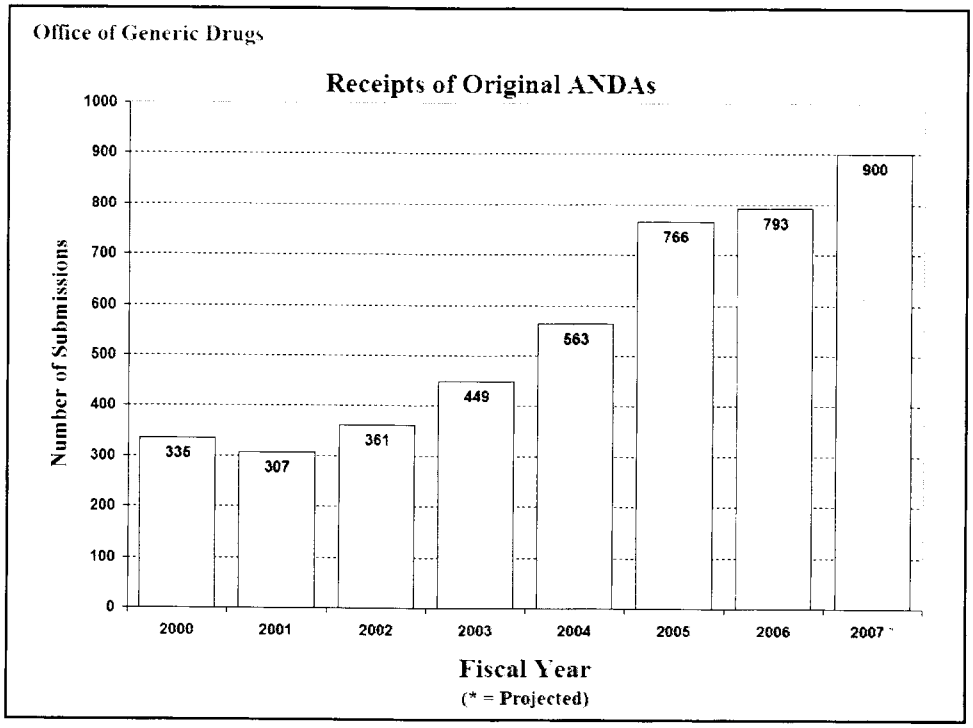

Division of Labeling &
Program Support
W. Peter Rickman
Director
<vacant>
Deputy Director
Vacant
Division Secretary
Review Support Branch
Tim Ames
Br. Chief
Regulatory Support Branch
CDR Martin Shimer
Br. Chief
Orange Book Staff
Robert Reinwald
Team Leader
Labeling Team 1
CAPT Lillie Golson
Team Leader
Labeling Team 2
John Grace
Team Leader
FY 2007
7

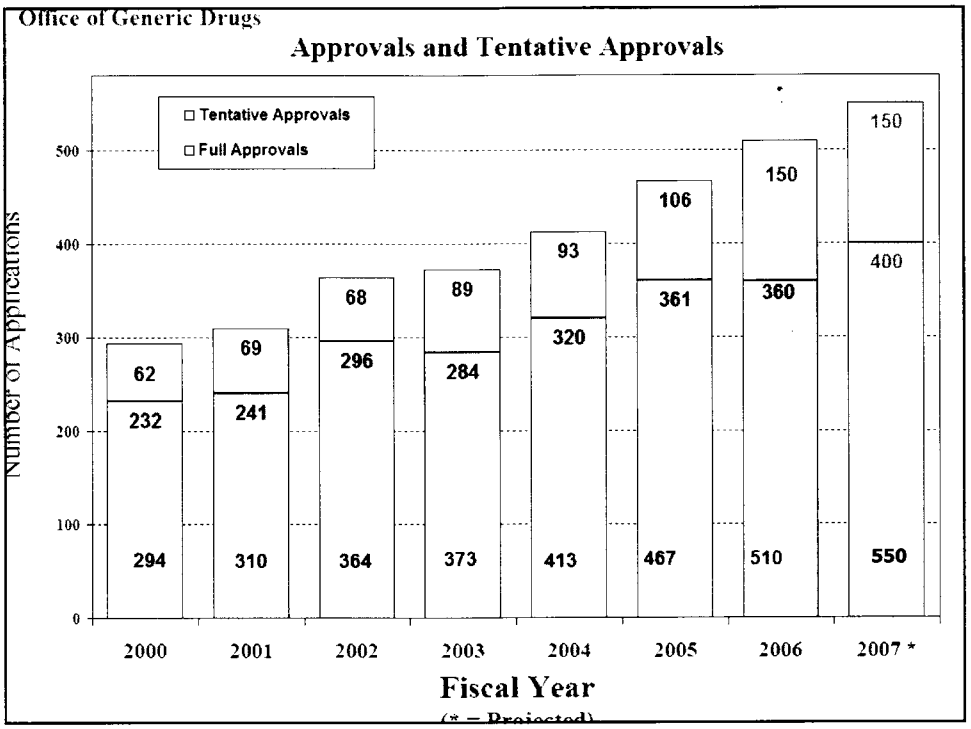

Division of Chemistry I
Rashmi Patel, Ph.D.
Director
Paul Schwartz, Ph.D.
Deputy Director
Vacant
Division Secretary
Team 1
Albert Mueller, Ph.D.
Team Leader
Team 2
Mike Smela
Team Leader
Team 3
James Fan
Team Leader
Team 5
Raj Bykadi, Ph.D.
Team Leader
Team numbers are COMIS designations
FY 2007
8

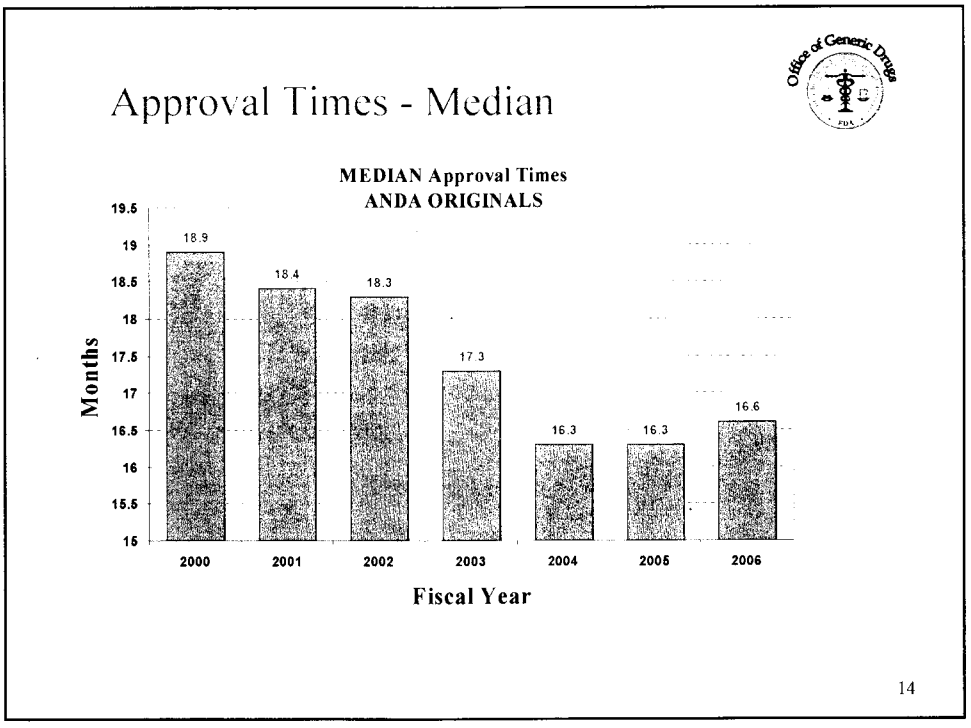

Division of Chemistry II
Florence Fang
Director
Richard Adams
Deputy Director
Rebacca Decker
Division Secretary
Team 7
M. Scott Furness, Ph.D.
Team Leader
Team 8
Ubrani Venkataram, Ph.D.
Team Leader
Team 9
Glen J. Smith
Team Leader
Team 10
Naiqi Ya, Ph.D.
Team Leader
Team numbers are COMIS designations
FY 2007
9


Division of Chemistry III
Vilayat Sayeed, Ph.D.
Director
Deputy Director
- vacant -
Edward Washington
Division Secretary
Team 4
Devinder Gill, Ph.D.
Team Leader
Team 6
Susan Zuk, Ph.D. (acting)
Team Leader
Team 11
Shing H. Liu, Ph.D.
Team Leader
Team 12
Hossein Khorshidi
Team Leader
Team numbers are COMIS designations
FY 2007
10

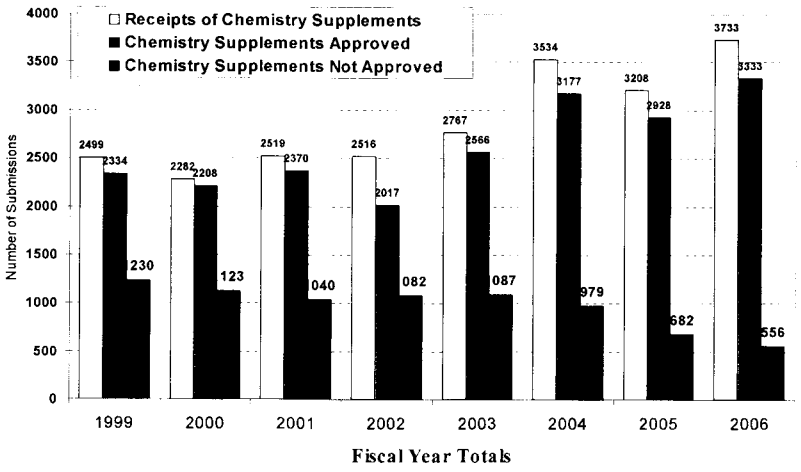

Division of Bioequivalence
Dale Conner, Pharm.D.
Director
Barbara Davit, Ph.D.
Deputy Director
Ra Chouk
Division Secretary
Team 3
Chandra Chaurasia, Ph.D.
Team Leader
Team 5
Kuldeep Dhariwal, Ph.D.
Team Leader
Team 2
Shiriniwas Nerurkar, Ph.D.
Team Leader
Team 4
Yih-Chain Huang, Ph.D.
Team Leader
Team 1
Moheb Makary, Ph.D.
Team Leader
FY 2007
11


Office of Generic Drugs
Receipts of Original ANDAs
Number of Submissions
1000
900
800
700
600
500
400
300
200
100
0
335
307
361
449
563
766
793
900
2000
2001
2002
2003
2004
2005
2006
2007
Fiscal Year
(* = Projected)


Office of Generic Drugs
Approvals and Tentative Approvals
Tentative Approvals
Full Approvals
Number of Applications
0
100
200
300
400
500
62
232
294
69
241
310
68
296
364
89
284
373
93
320
413
106
361
467
150
360
510
150
400
550
2000
2001
2002
2003
2004
2005
2006
2007 *
Fiscal Year
(* = Projected)


Approval Times - Median
Office of Generic Drugs
MEDIAN Approval Times
ANDA ORIGINALS
Months
15
15.5
16
16.5
17
17.5
18
18.5
19
19.5
18.9
18.4
18.3
17.3
16.3
16.3
16.6
2000
2001
2002
2003
2004
2005
2006
Fiscal Year
14

ANDA Chemistry Supplements



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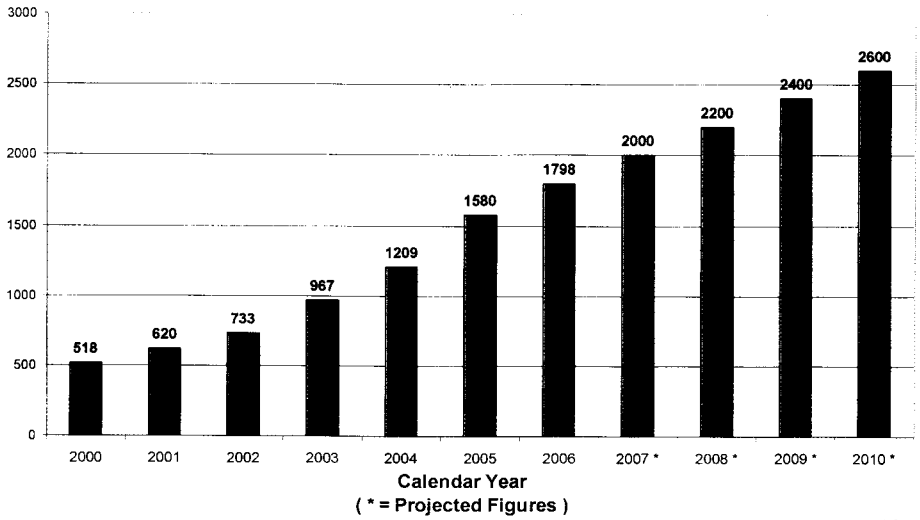
OGD Controlled Correspondence Documents Received



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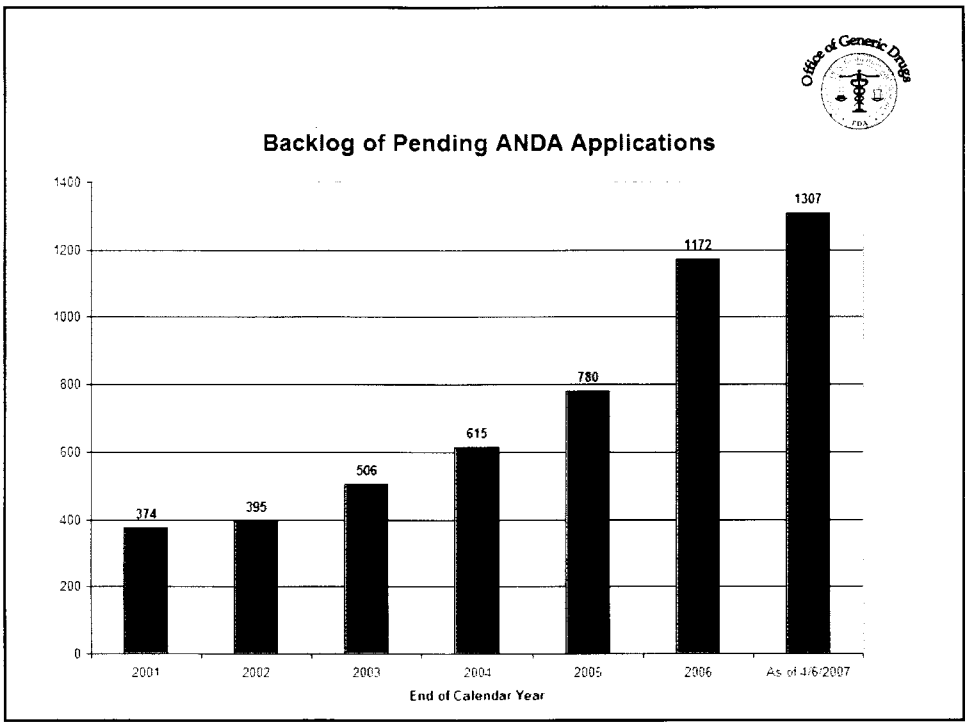

Important First Generic Approvals – 2007

- FENTANYL TRANSDERMAL SYSTEM, 12 MCG/HOUR (Duragesic-12)
- PROPRANOLOL HCL EXTENDED-RELEASE CAPSULES (Inderal LA)
- DEXMETHYLPHENIDATE HCL TABLETS (Focalin)
- VALACYCLOVIR HCL TABLETS (Valtrex)
- SERTRALINE HCL TABLETS (Zoloft)
- RABEPRAZOLE SODIUM DELAYED-RELEASE TABLETS (Aciphex)
- RANITIDINE ORAL SOLUTION USP (Zantac Syrup)
- CITALOPRAM HBR CAPSULES (Celexa)
- MOEXIPRIL HCL AND HYDROCHLOROTHIAZIDE TABLETS (Uniretic)
- DIDANOSINE FOR ORAL SOLUTION (PEDIATRIC POWDER), (Videx)
- PREDNICARBATE OINTMENT (Dermatop)
- CIPROFLOXACIN EXTENDED-RELEASE TABLETS (Ciprox XR)
- NADOLOL AND BENDROFLUMETHIAZIDE TABLETS USP, (Corzide)
- CEFIXIME FOR ORAL SUSPENSION USP (Cefixime)
- NIMODIPINE CAPSULES (Nimotop)
- ZOLPIDEM TARTRATE TABLETS (Ambien)
- PRAVASTATIN SODIUM TABLETS (Pravachol)
- METOPROLOL SUCCINATE EXTENDED-RELEASE TABLETS USP (Toprol XL)
- PAROXETINE HCL EXTENDED-RELEASE TABLETS (Paxil CR)

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NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	Generic Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

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NDA vs. ANDA Review Process

- NDA Review = Lower volume (ave. 25 approvals/year), but Higher Complexity (Pre-Clinical, Clinical Trials, etc.)
- ANDA Review = Higher volume (425 approvals/year), but Lower Complexity (Safety & Efficacy already established)

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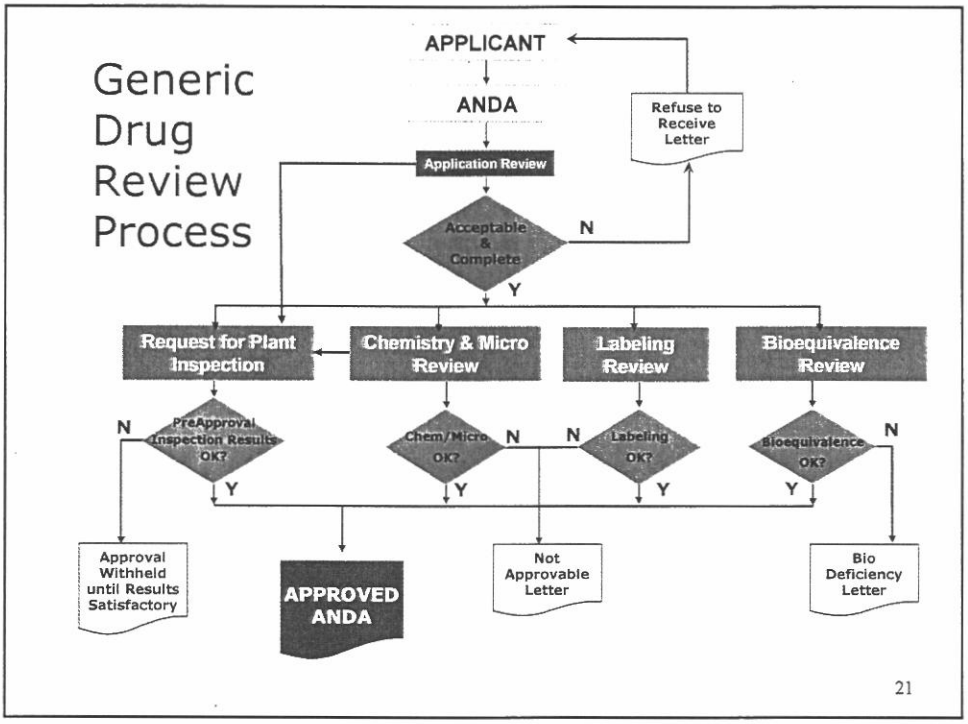
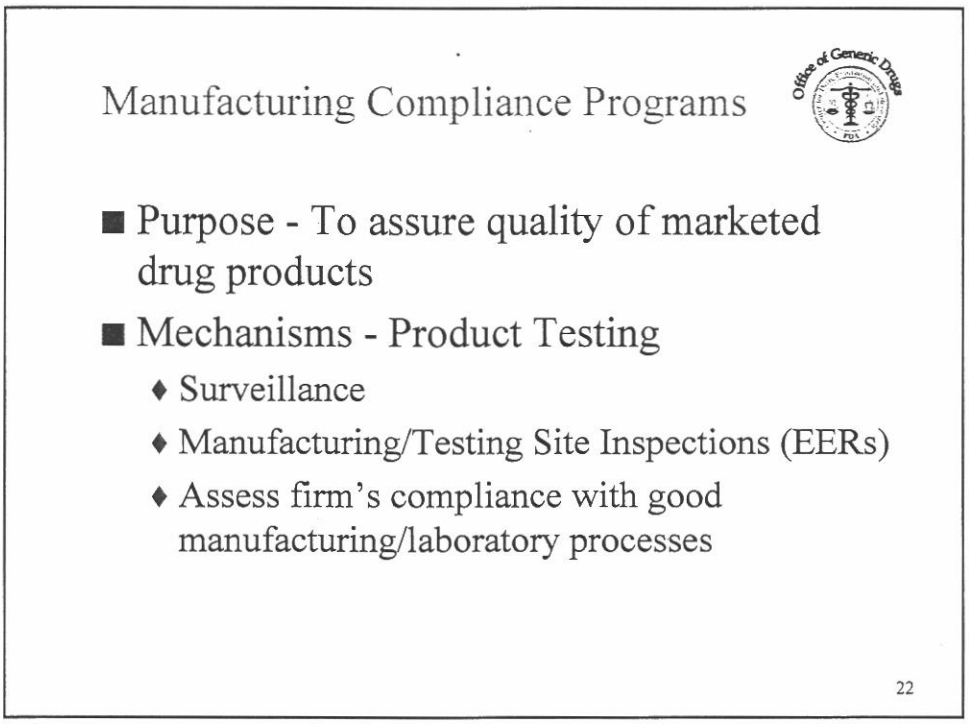

Generic Drug Review Process
APPLICANT
ANDA
Application Review
Refuse to Receive Letter
Acceptable & Complete
N
Y
Request for Plant Inspection
Chemistry & Micro Review
Labeling Review
Bioequivalence Review
N
PreApproval Inspection Results OK?
Chem/Micro OK?
N
N
Labeling OK?
Bioequivalence OK?
N
Y
Y
Y
Y
Approval Withheld until Results Satisfactory
APPROVED ANDA
Not Approvable Letter
Bio Deficiency Letter
21


Manufacturing Compliance Programs
Office of Generic Drugs
■ Purpose - To assure quality of marketed drug products
■ Mechanisms - Product Testing
♦ Surveillance
♦ Manufacturing/Testing Site Inspections (EERs)
♦ Assess firm's compliance with good manufacturing/laboratory processes
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Chemistry Review

- Components and composition
- Manufacturing and controls
- Batch formulation and records
- Description of facilities
- Specs and tests
- Packaging
- Stability

23

Labeling Review

- "Same" as brand name labeling
- May delete portions of labeling protected by patent or exclusivity
- May differ in excipients, PK data and how supplied

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Definition of Bioequivalence (BE)

Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions

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Purpose of BE Review

- Therapeutic equivalence (TE)
- Bioequivalent products can be substituted for each other without any adjustment in dose or other additional therapeutic monitoring
- The most efficient method of assuring TE is to assure that the formulations perform in an equivalent manner

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Clinical Review Staff

- Dr. Dena Hixon, M.D.
- Reviews bioequivalence studies with clinical endpoints
- Evaluates safety issues (inactive ingredients, adverse events, etc.)
- Assesses clinical issues in ANDAs (effect of different vehicles, inactive ingredients)
- Assesses equivalence challenges

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OGD Project Manager Role

- Discipline specific PMs
- Review process based on **First-In = First-Reviewed** – Not PDUFA
- Chemistry review drives the review process; hence, Chemistry PM monitors overall review progress
  - ♦ Ex: Informs Bioequivalence/Microbiology PM of need for reviews
  - ♦ Prepares full approval package

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OGD Project Manager Role

- Bioequivalence PM
  - Controlled correspondence
  - Bioequivalence waiver requests
  - Bioequivalence review queues
- Microbiology PM
  - Monitors review queue
  - Assures ANDAs needing microbiology review are identified

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OGD Project Manager Role

- All fulfill other traditional PM functions, e.g., communication with industry, assuring all actions are documented

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Research Initiatives by OGD Scientific Staff
Lawrence Yu, Ph.D., Director for Science

- Respond to Scientific Challenges
- Develop Bioequivalence Methods
  - MDIs
  - Topicals
  - Injectable Suspensions
- Expand In-House Capabilities
- Work with Office Testing & Research in developing/hiring expertise
- External Contracts

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"Orange Book Staff"

- "Approved Drug Products with Therapeutic Equivalence Evaluations"
- All FDA approved drug products listed (NDA's, OTC's & ANDA's)
  - Therapeutic equivalence codes
    - → "A" = Substitutable
    - → "B" = Inequivalent, NOT Substitutable
  - Expiration dates: patent and exclusivity
  - Reference Listed Drugs/brand drugs identified by FDA for generic companies to compare with their proposed products

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OGD Education Committee

- Purpose – To provide educational offerings for the OGD staff including training and plant visits
- Committee has at least one member from each OGD review discipline
- Plant trips
- OGD Reviewer Forum
- Workshops – Open to others on space available basis

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New Drug Review Divisions Interactions with OGD

- Bundled Reviews
- Consults
- Risk Management/Educational Programs
- Labeling Supplements
- Best Pharmaceuticals for Children Act (BPCA)
- OGD Website – Contact list

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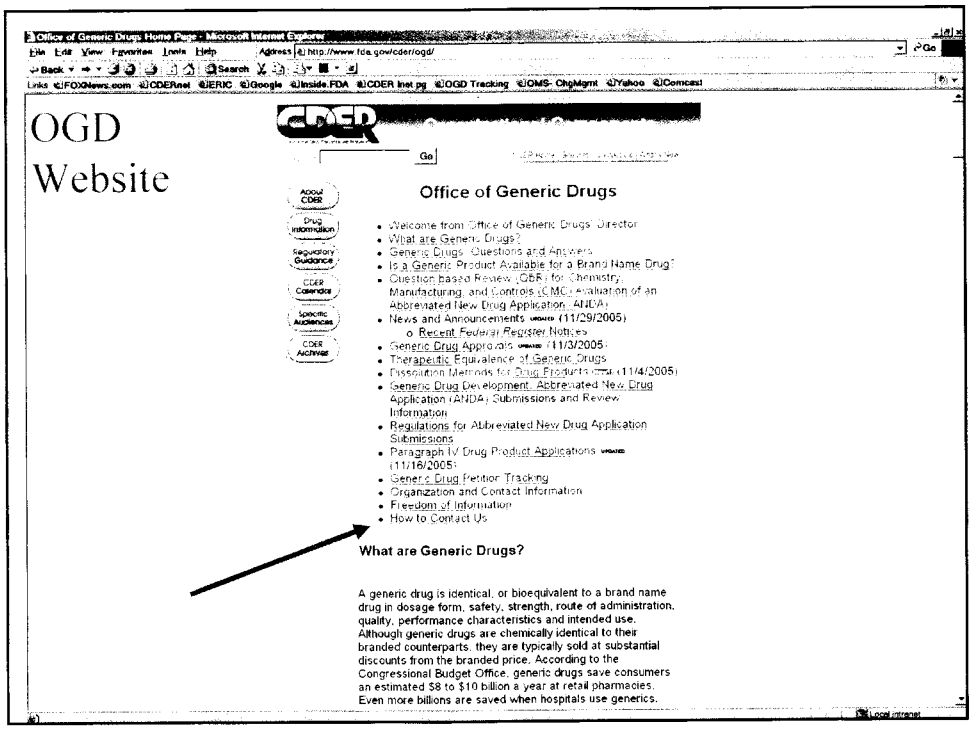
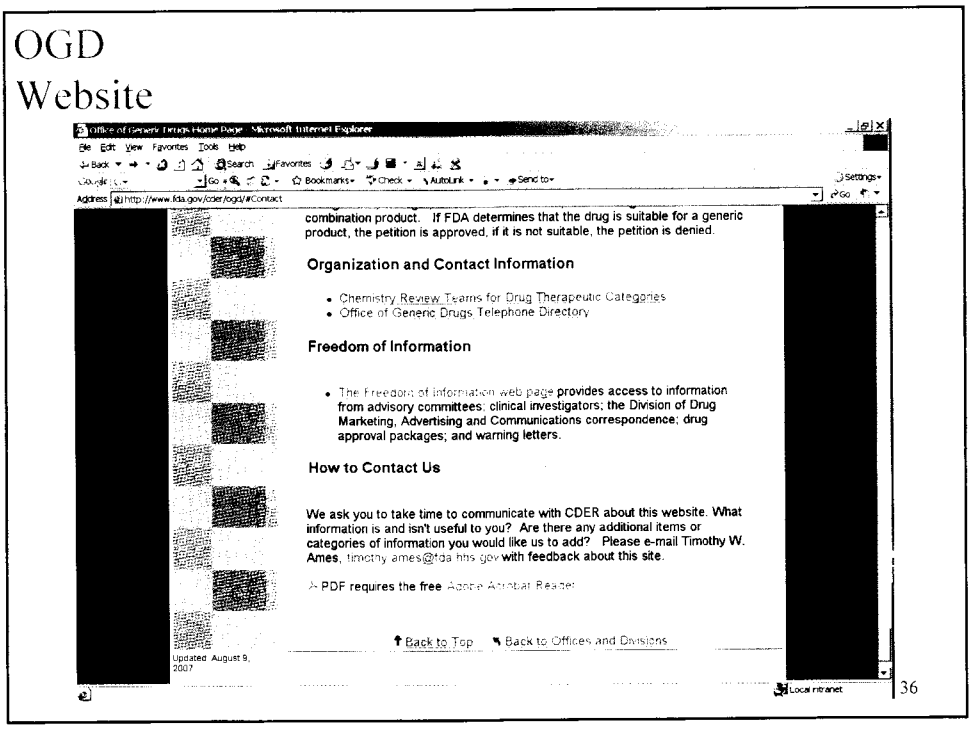

OGD
Website
Office of Generic Drugs
Welcome from Office of Generic Drugs' Director
What are Generic Drugs?
Generic Drugs: Questions and Answers
Is a Generic Product Available for a Brand Name Drug?
Question-based Review (QBR) for Chemistry, Manufacturing, and Controls (CMC) Evaluation of an Abbreviated New Drug Application (ANDA)
News and Announcements (11/29/2005)
Recent Federal Register Notices
Generic Drug Approvals (11/3/2005)
Therapeutic Equivalence of Generic Drugs
Dissolution Methods for Drug Products (11/4/2005)
Generic Drug Development, Abbreviated New Drug Application (ANDA) Submissions and Review Information
Regulations for Abbreviated New Drug Application Submissions
Paragraph IV Drug Product Applications (11/16/2005)
Generic Drug Petition Tracking
Organization and Contact Information
Freedom of Information
How to Contact Us
What are Generic Drugs?
A generic drug is identical, or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics.


OGD
Website
combination product. If FDA determines that the drug is suitable for a generic product, the petition is approved, if it is not suitable, the petition is denied.
Organization and Contact Information
Chemistry Review Teams for Drug Therapeutic Categories
Office of Generic Drugs Telephone Directory
Freedom of Information
The Freedom of Information web page provides access to information from advisory committees; clinical investigators; the Division of Drug Marketing, Advertising and Communications correspondence; drug approval packages; and warning letters.
How to Contact Us
We ask you to take time to communicate with CDER about this website. What information is and isn't useful to you? Are there any additional items or categories of information you would like us to add? Please e-mail Timothy W. Ames, timothy.ames@fda.hhs.gov with feedback about this site.
PDF requires the free Adobe Acrobat Reader
Back to Top
Back to Offices and Divisions
Updated August 9, 2007
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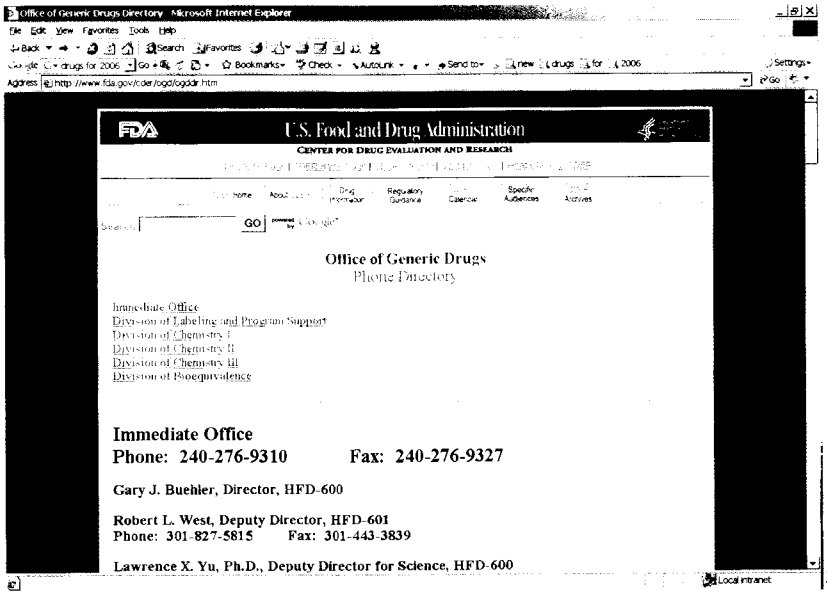
OGD Website



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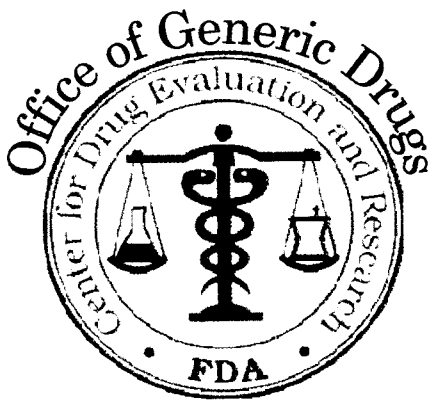

7500 Standish Place (HFD-600)
Rockville, MD 20855
240-276-9310

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Impact of USP Monographs on the Office of Generic Drugs Review Process

October 1, 2007

Frank O. Holcombe, Jr., Ph.D.
Associate Director for Chemistry
Office of Generic Drugs

USP/NF

United States Pharmacopeial Convention

- **Promote Public Health Through Authoritative Standards and Information**
- **United States Pharmacopeia and National Formulary**
- **Independent**
- **Public Process**
- **Non-Governmental**

United States Pharmacopeia & National Formulary

The Official Compendia of Standards

Organization

- **General Notices**
- **Official Monographs**
- **General Chapters**

- **National Formulary**

USP/NF

Monographs

- **Official Articles**
  - **Drug Substance**
  - **Inactive Ingredient (excipients)**
  - **Drug Product**

- **Official drug products/devices**
  - **Ingredients meet Compendial Monographs**

USP/NF

Monograph

Drug Substance Parameter Examples

- *** Description**
- *** Packaging and Storage**
- *** Reference Standards (as available)**
- *** Identification**
- **Residue on Ignition**
- **Heavy Metals**
- **Organic Volatile Impurities**
- **Chromatographic Purity**
- **Water/Loss on Drying**
- *** Assay**

USP/NF

Monograph

Drug Product Parameter Examples

- *** Description**
- *** Packaging and Storage**
- *** Reference Standards (as available)**
- *** Identification**
- **pH**
- **Dissolution**
- *** Uniformity of Dosage Units**
- **Related Compounds**
- **Water/Loss on Drying**
- *** Assay**

USP/NF

Food Drug and Cosmetic Act

Section 201 (g)(1) - "drug" means

- **(A) articles recognized in the official United States Pharmacopeia, ... National Formulary....**
- **(D)articles intended for use as a component of any articles specified in (A)....**

Section 501(b) - Adulterated Drugs

- **Strength, Quality, Purity**

Section 502(e), (g) - Misbranded Drugs

- **Established Name; Packaging**

USP/NF

Title 21 - Code of Federal Regulations

Section 314.50(d)(1) - Chemistry, manufacturing, and controls

- **Drug Product, Drug Substance -**
  - **Reference to ... U.S. Pharmacopeia ... may satisfy relevant requirements of this paragraph.**

Section 314.50(e) - Samples and labeling

- **Reference standards recognized ... official compendium ...**

USP/NF

Monograph

Concern - **Identity**
- **Quality**
- **Strength**
- **Purity**

Provides - **Tests**
- **Methods**
- **Acceptance Criteria**

USP/NF Monograph		**Application Review Goals**	
Concerns	- **Identity**	**Concerns**	- **Identity**
	- **Quality**		- **Quality**
	- **Strength**		- **Strength**
	- **Purity**		- **Purity**
			- **Bioequivalence**
Provides	- **Tests**	**Evaluate**	- **Tests**
	- **Methods**		- **Methods**
	- **Acceptance Criteria**		- **Acceptance Criteria**

USP/NF

Application Review Goals

Additional Concerns

- **Manufacturing**
- **Development**
- **Scale Up**
- **Non-USP materials**
- **Non-USP attributes**

USP/NF

Review Process

- **Monograph**
  - ***Required* Criteria**
  - **Provides Defined Methods**
  - **Provides Basis for Standard Procedures**
  - **Provides Structure for Generalized Acceptance Criteria**
  - **A *Partial* Basis for Specification Setting**

USP/NF

Review Process Issues

- **Monograph • A *Partial* Basis for Specification Setting**
  - **Criteria are Official**
  - **Defined for Release and Shelf Life**
    - **Stability Indicating Methods?**
  - **Criteria are Generally Process-specific**
  - **Single source vs Multi-source**
    - **Impurities/Degradants**
    - **Substitution**
  - **Multiple Methods**

USP/NF

Monograph at Time of Application Approval

Year	Drug Substance	Drug Product	Distinct DS (% total app)
1997	60 %	35 %	44 %
1998	59 %	57 %	53 %
1999	80 %	61 %	58 %
2000	75 %	62 %	68 %
2004*	------	48%	------

*January - June

USP/NF

Change Process

Pharmacopeial Forum

Topics - New Monograph

- Revised Monograph

- General Chapters

USP/NF

Change Process

Compendial Operations Staff

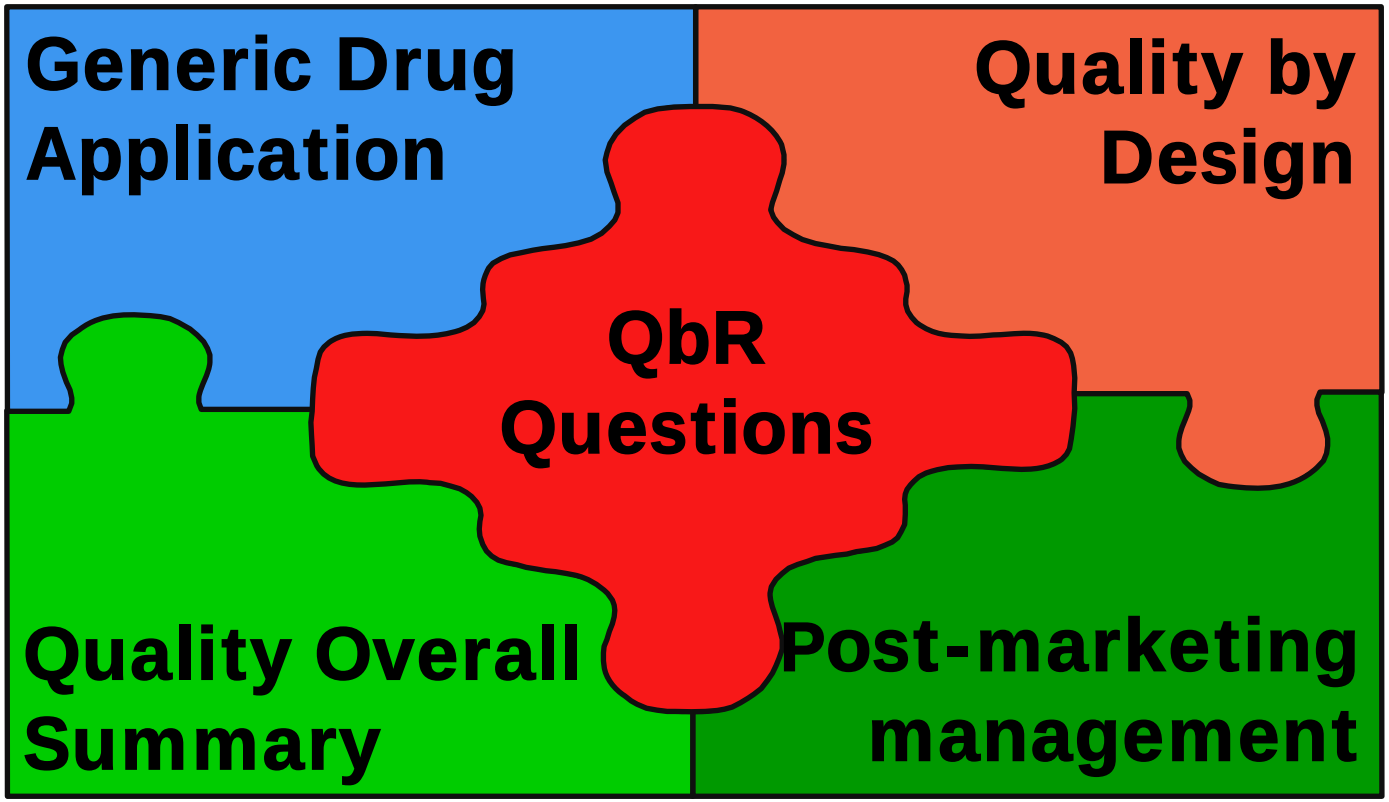
- **Monitor USP Proposals**
- **Information Conduit**
- **Responsible for Official Comment**
- **Formal Contact with USP**

Question-based Review: Implementing Quality by Design

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

Opinions expressed in this presentation are those of the speakers and do not necessarily reflect the views or policies of the FDA

QbR is a System



Pharmaceutical Quality

$= f$ (Drug Substance, Excipients, Manufacturing, and Packaging)

Janet Woodcock on QbD

J. Woodcock.
***Am. Pharm. Rev.*,**
2004

- ***Quality by Design*** **"means that product and process performance characteristics are scientifically designed to meet specific objectives... To achieve QbD objectives, product and process characteristics important to desired performance must be derived from a combination of prior knowledge and experimental assessment during product development."**

ICH Q8 Describes Quality by Design

- **Introduced in ICH Q8**
  - **"*quality* cannot be tested into products, i.e., quality should be built in by design"**
- **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**

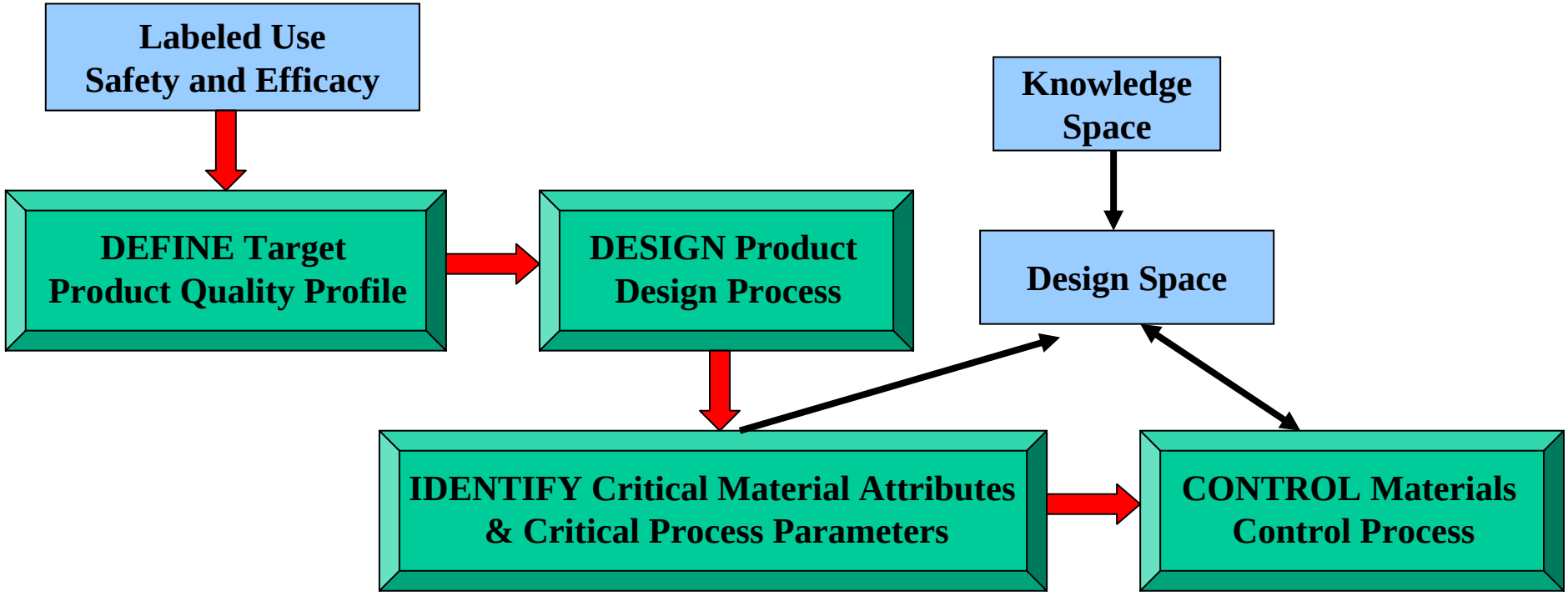
ISPE PQLI on QbD, Sept. 14, 2007

- **Quality by Design is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding based on sound science and quality risk management. This approach entails the following aspects:**
  - **Defining the desired product performance, or more generally the Pharmaceutical Target Product Profile**
  - **Identifying those product characteristics that are Critical Quality Attributes (CQAs)**
  - **Identifying process parameters and material attributes that can affect CQAs**
  - **Creating or using an established Knowledge Space to establish one or more Design Space(s) and an appropriate Control Strategy that reliably deliver a product that meets requirements**
  - **Incorporating the approach into the business plan, product development plan, and assuring and enabling it through the Quality System to facilitate continual improvement throughout the product lifecycle**

What is Quality by Design?

- **Quality by Design means**
  - **designing and developing formulations and manufacturing processes to ensure a predefined quality**
- **Quality by Design requires**
  - **understanding how formulation and manufacturing process variables influence product quality**
- **Quality by Design ensures**
  - ***Product quality (along with ICH Q9 and Q10)***

Overview of QbD



TARGET → DESIGN → IMPLEMENTATION

QbD to an FDA Generic Drug Reviewer

- **Defining target product quality profile**
  - **The performance needed to get clinical benefit and meet consumer expectation**
- **Designing product and processes to meet target product quality profile**
- **Identifying critical material attributes, process parameters, and sources of variability**
  - **Design space**
- **Controlling materials and manufacturing processes to produce consistent quality over time**

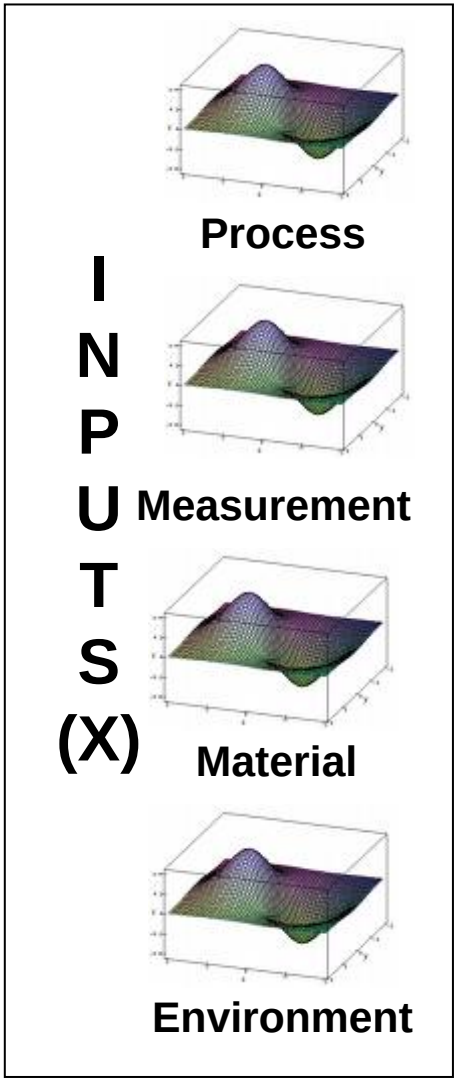
Target Product Quality Profile: Beginning the Drug Development with the End in Mind

- **FDA's recent guidance on Target Product Profile (TPP)**
- **The Target Product Quality Profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process**
- **ISPE PQLI: Pharmaceutical Target Product Profile**
- **TPQP: Example**
  - **Assay (uniformity)**
  - **Purity**
  - **Stability**
  - **Desired pharmacokinetic profile**
    - **In vitro dissolution**
    - **Bioequivalence**

Designing Product and Processes to Meet Target Product Quality Profile

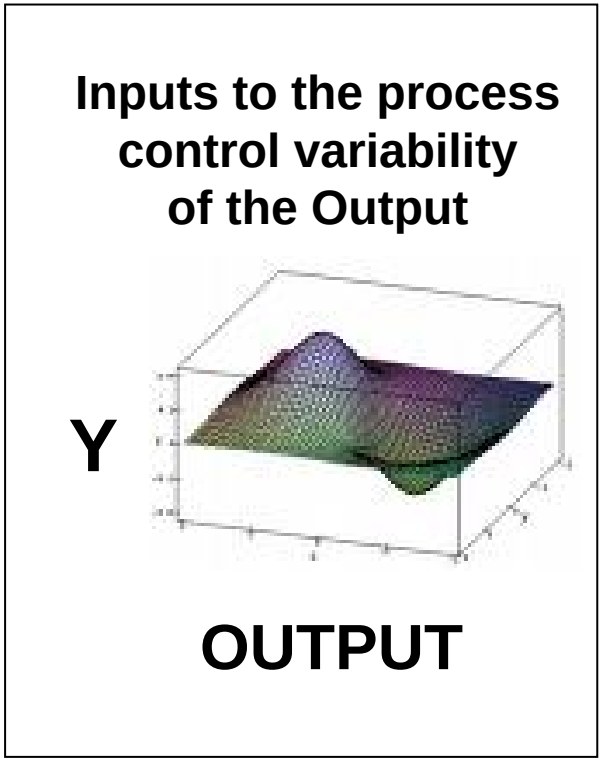
- **Product Design**
  - **Physical, chemical, and biological properties of drug substance**
  - **Biopharmaceutics Classification System (BCS) and formulation development**
- **Process Design**
  - **Mechanical properties, flow properties, and others**
  - **Unit operation selection**
  - **Identification of process parameters and material attributes**

Identifying Critical Material Attributes, Process Parameters, and Sources of Variability



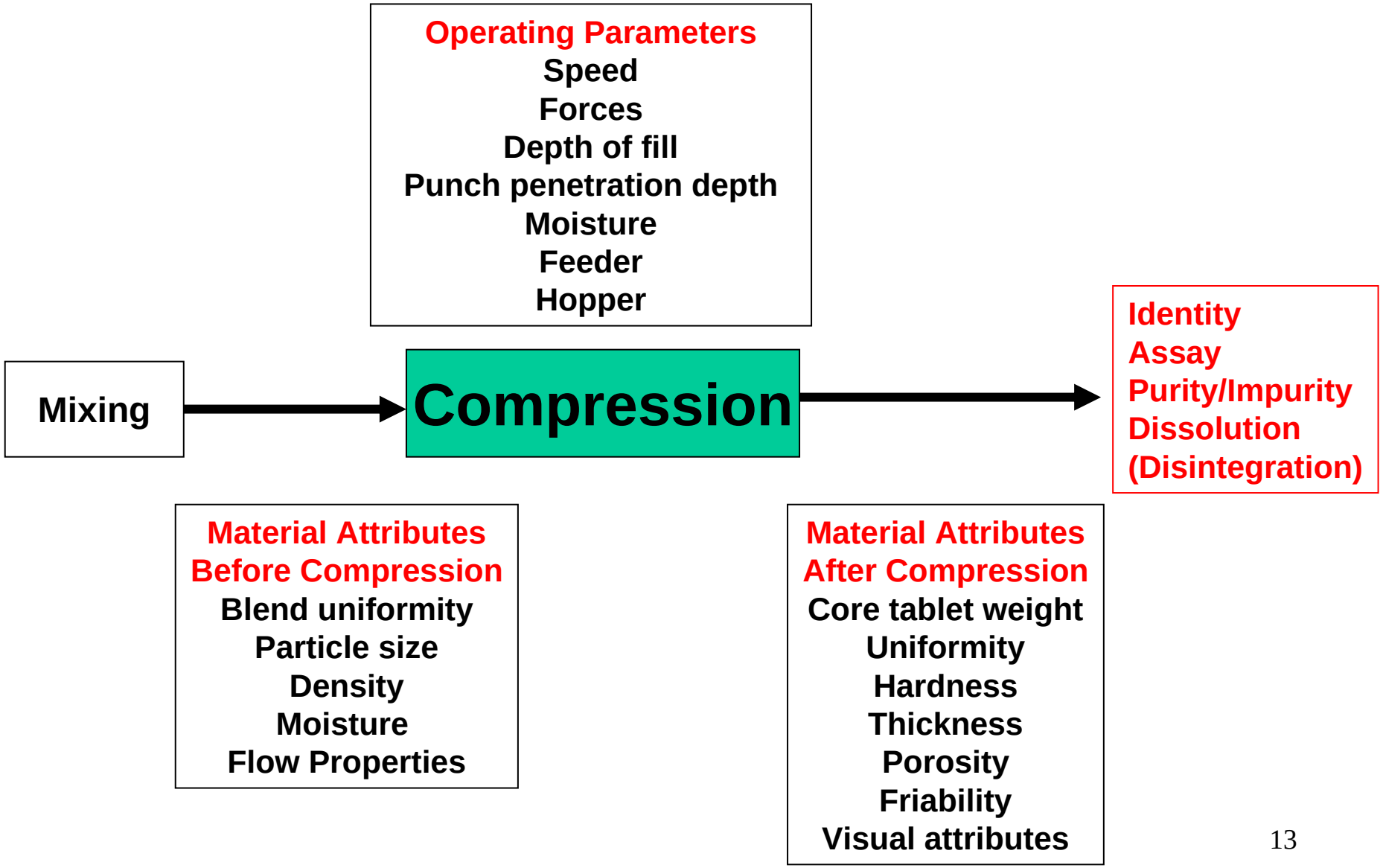
$Y = f(X)$

Priori knowledge
Risk Assessment
Design of Experiments



Material Attributes

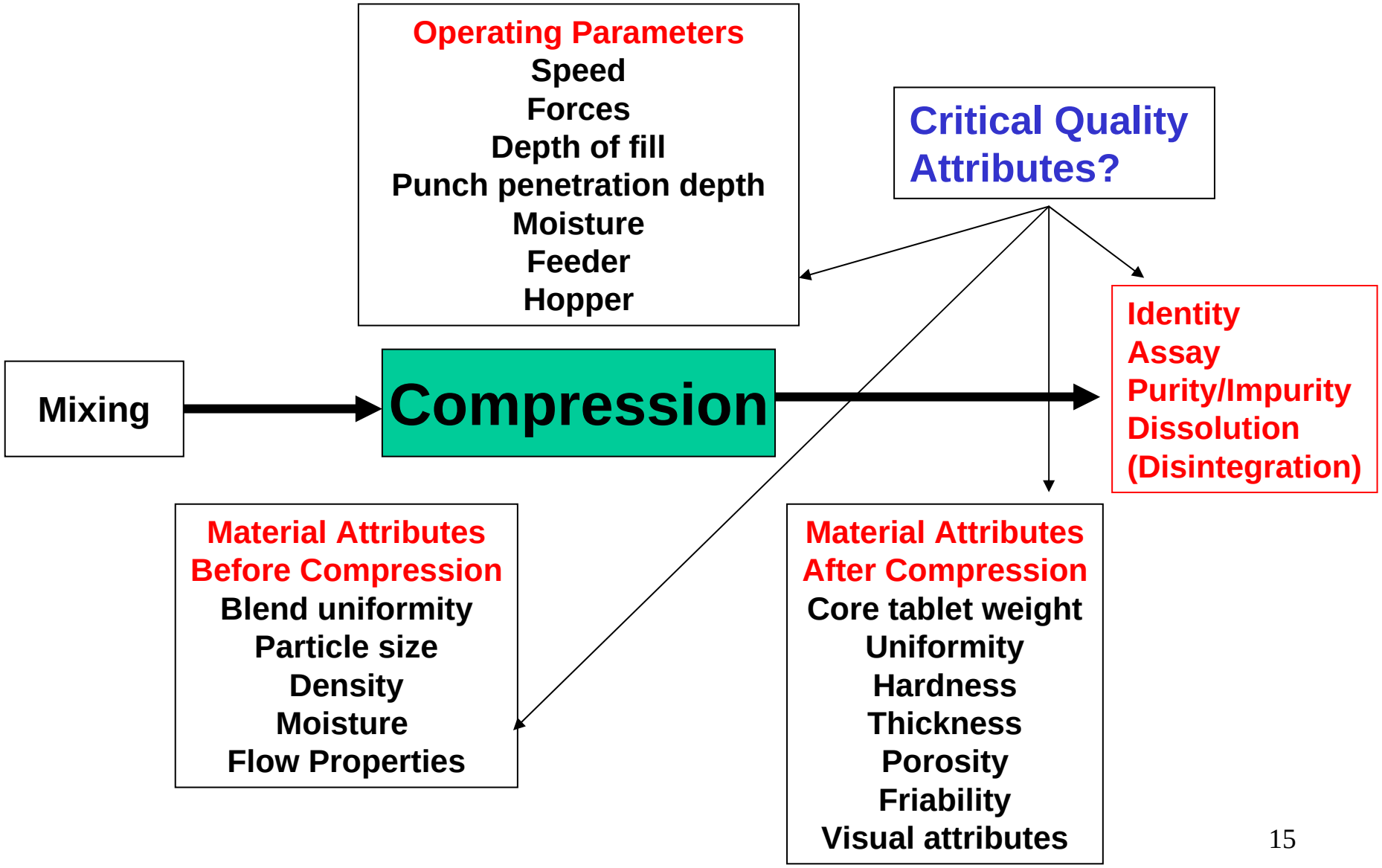
Process Understanding: An Example



Critical Quality Attribute?

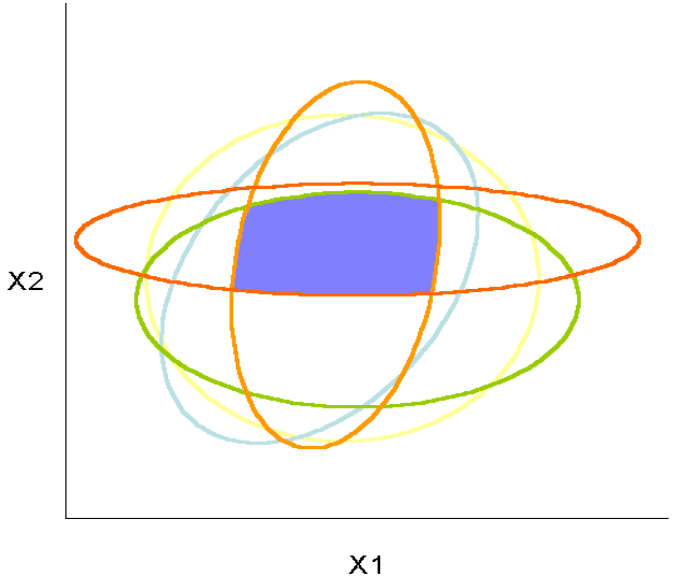
- **“A critical quality attribute is a physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality.”**
- **“An attribute is a quality or characteristic inherent in or ascribed to something. It may be measurable properties of a material, or *measurable characteristics of the process* to make the material.”**

Process Understanding: An Example



Design Space

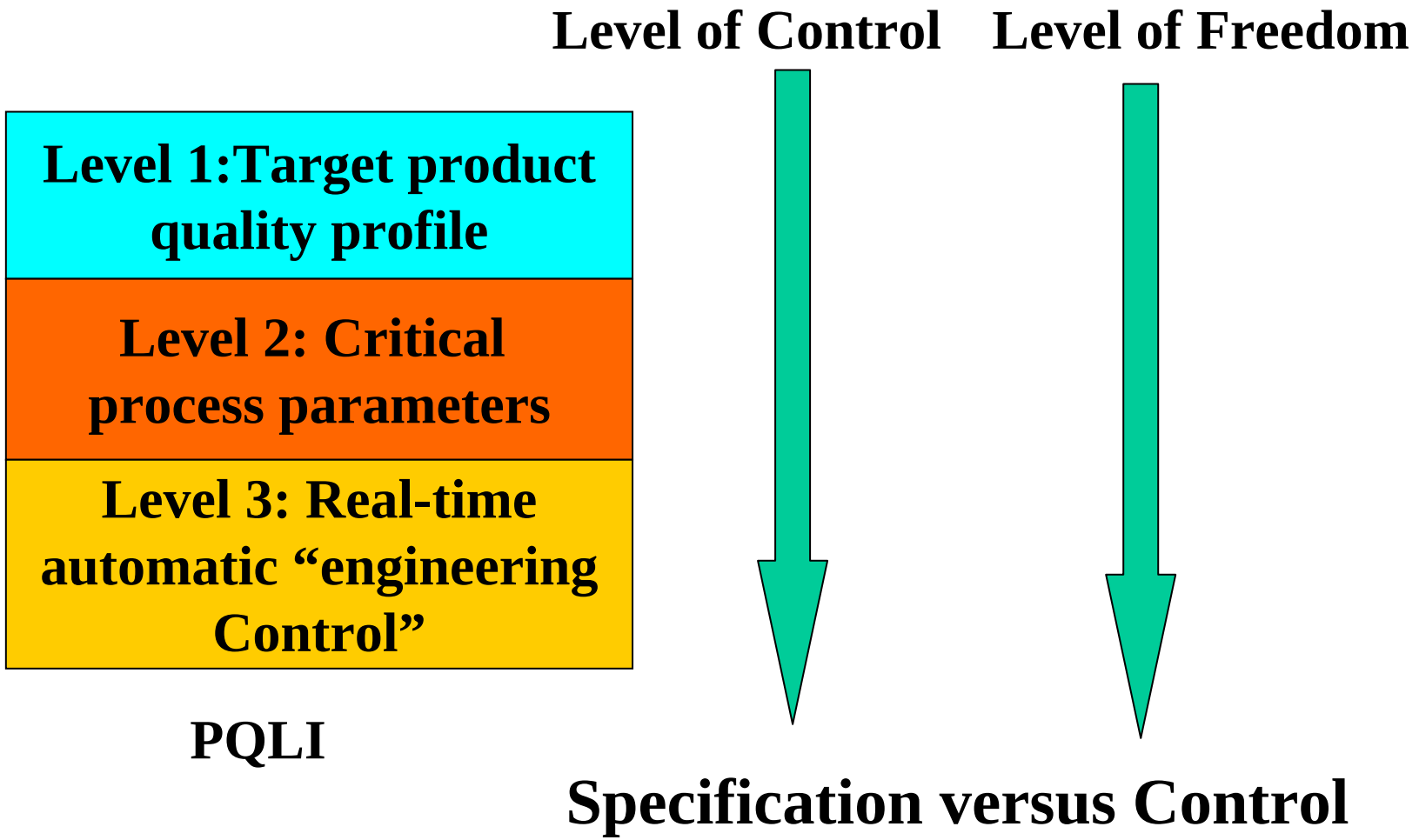
- **Design Space**
  - **The <u>multidimensional</u> combination and interaction of input variables (eg. Material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process.**
- **Design space is often established based on *in vitro* "predictive" dissolution**

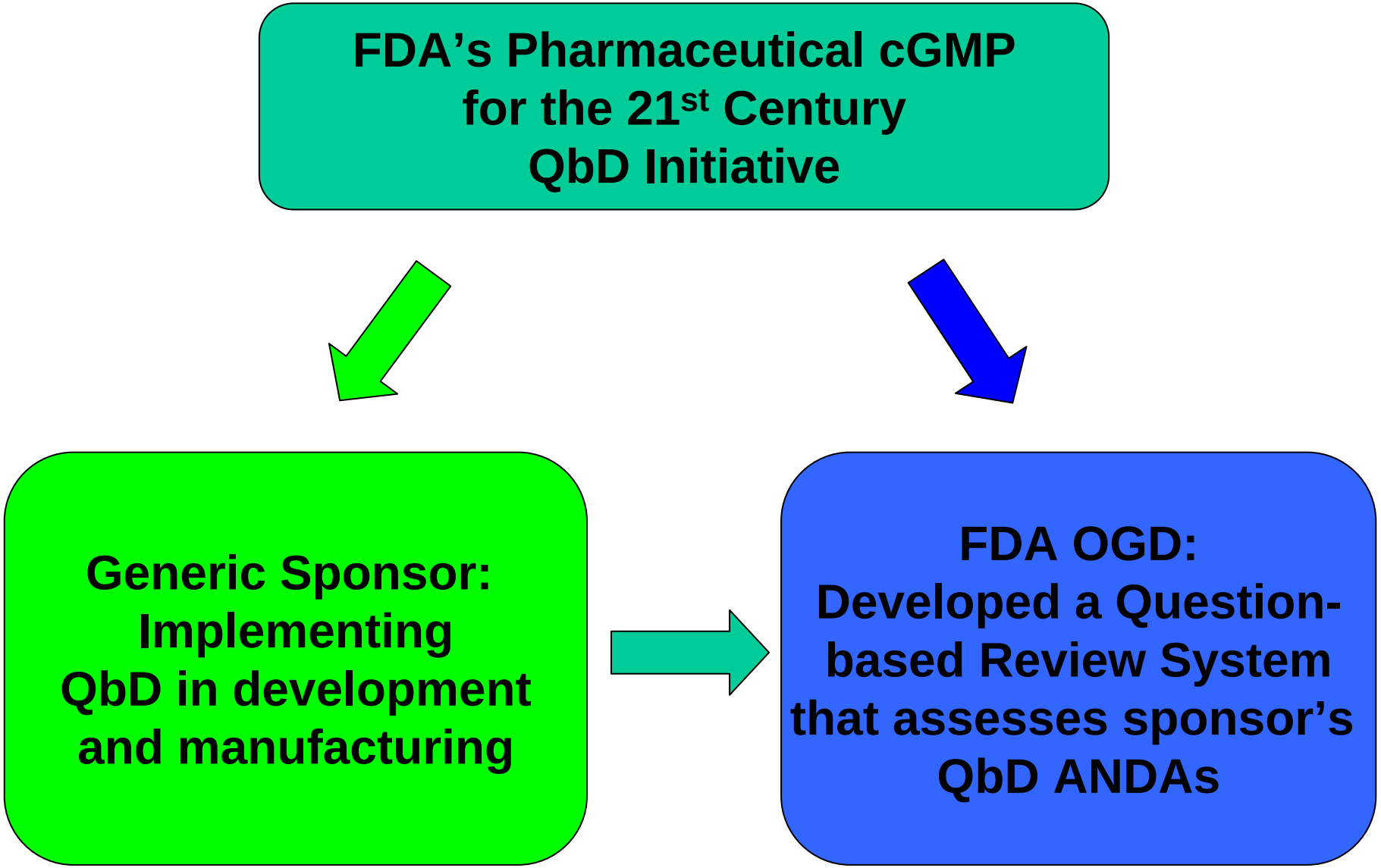


OGD on Design Space: A Proposal

- **Ranges for input materials and process parameters if there are no interactions among them**
- **Design space can be proposed at the ANDA filing approval**
  - **Priori knowledge,**
  - **Risk Assessment, and/or**
  - **Design of Experiments**
- **The proposed design space is subject to post approval confirmation**
  - **Annual Report**

Controlling Input Materials and Manufacturing Processes to Produce Consistent Quality over Time

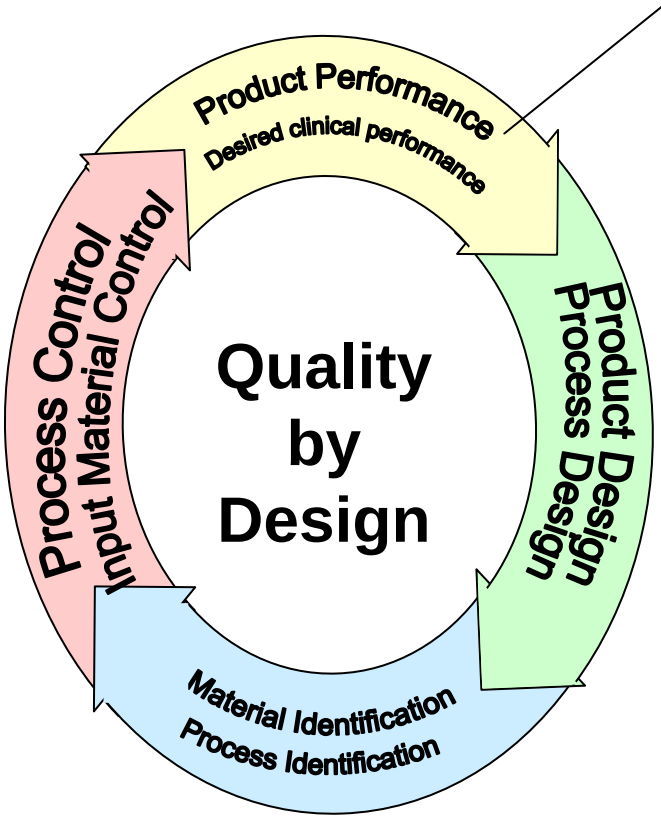



FDA's Pharmaceutical cGMP for the 21st Century QbD Initiative
Generic Sponsor: Implementing QbD in development and manufacturing
FDA OGD: Developed a Question-based Review System that assesses sponsor's QbD ANDAs

QbR Questions Provides a Roadmap

- **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**

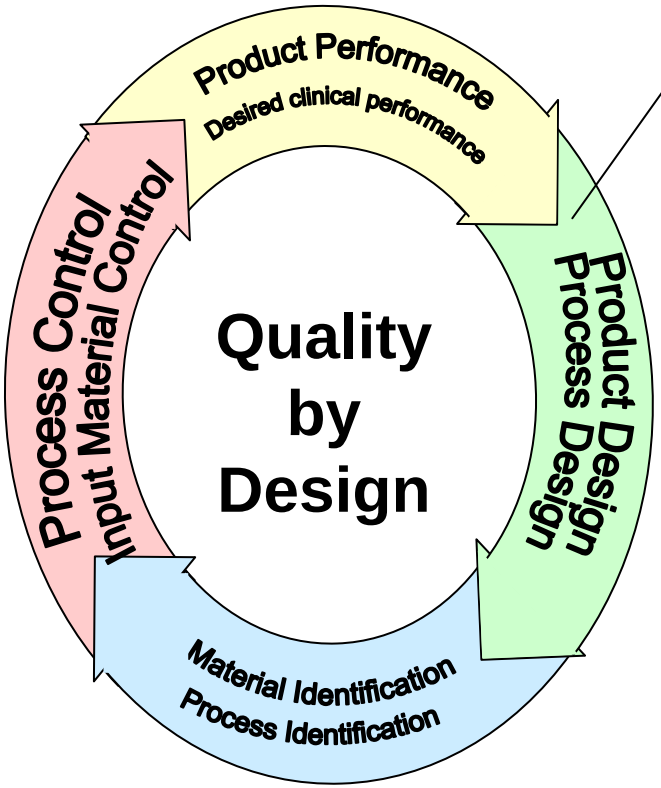
How Does QbR Implement QbD?
Product Performance



What attributes should the drug product possess?
Answer: What was the goal?

What does OGD mean by attributes in this question?
Answer: Target product quality profile such as assay, purity, dissolution, stability etc.

How Does QbR Implement QbD?
Product Design



How was the product designed to have these attributes?

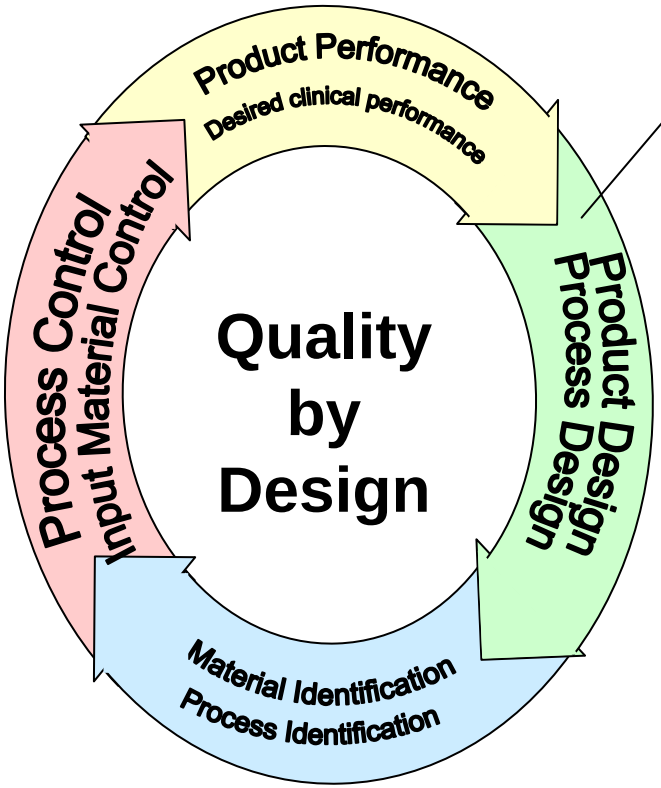
Were alternative formulations or mechanisms investigated?

How were the excipients selected?

How was the final formulation optimized?

Continuous Improvement

How Does QbR Implement QbD?
Process Design



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?

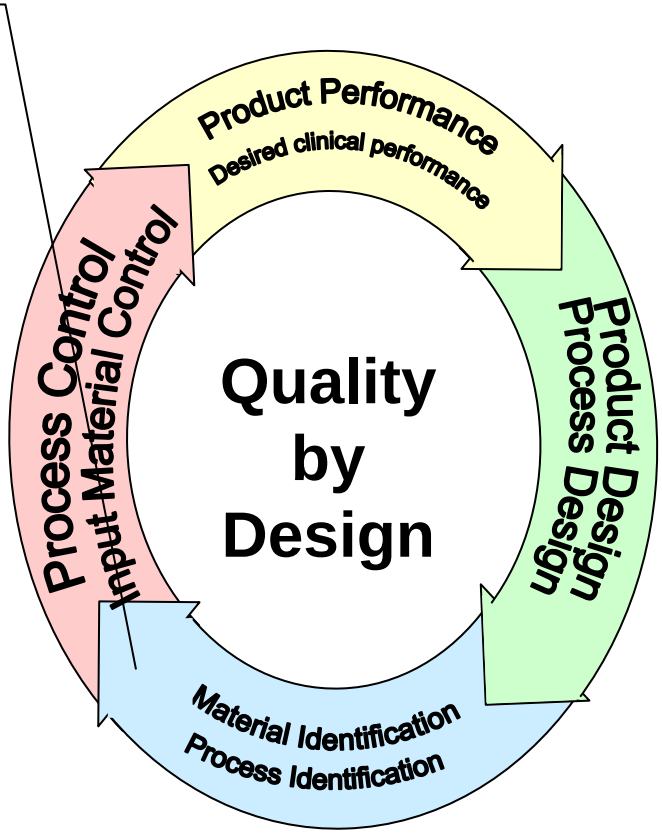
Continuous Improvement

How Does QbR Implement QbD?
Material and Process Identification

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?

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



Critical Material Attribute and Process Parameter

- A Critical Material Attribute is a physical, chemical, biological or microbiological property or characteristic of a material that needs to be controlled (directly or indirectly) to ensure product quality.

- A Critical Process Parameter is a process parameter whose variability impacts a quality (material) attribute and therefore needs to be controlled to ensure the process produces the desired quality. A critical process parameter remains critical even if it is controlled.

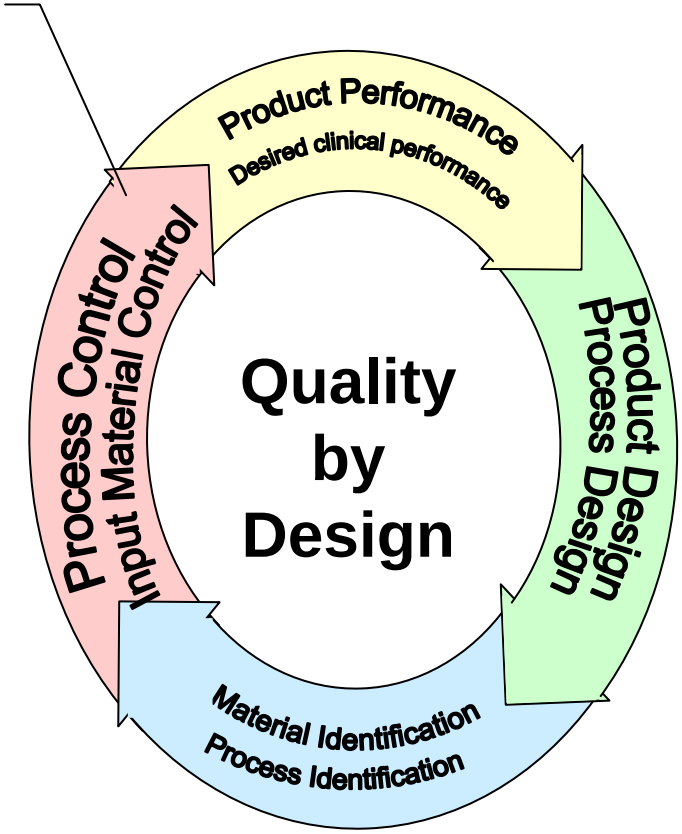
How Does QbR Implement QbD?
Process and Input Material Controls

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?



QbR Communications

- **www.fda.gov/cder/ogd/QbR.htm**
  - **QbR White Paper**
  - **QbR Questions**
  - **QbR Frequently Asked Questions**
  - **QbR mock examples**
  - **QbR updates**
- **Publications on QbR**
  - ***J. Generic Medicine, Pharm. Eng….***
- **Workshops, Webcast, and Teleconf.**

Conclusion

- **The FDA OGD has developed a Question-based Review for quality assessment. It is a concrete and practical implementation of the underlying concepts and principles outlined by the FDA's Pharmaceutical CGMPs for the 21st Century and Quality by Design (QbD) initiatives**

Questions to be completed by ANDA Sponsors for the preparation of a QbR-Quality Overall Summary

Pharmaceutical Product Quality: Question-based Review for ANDAs

Definition: Simple Dosage Form - Either a solution or an IR solid oral dosage form

2.3 Introduction to the Quality Overall Summary

Proprietary Name of Drug Product

Non-Proprietary Name of Drug Product

Non-Proprietary Name of Drug Substance

Company Name

Dosage Form

Strength(s)

Route of Administration

Proposed Indication(s)

2.3.S DRUG SUBSTANCE

2.3.S.1 General Information

What are the nomenclature, molecular structure, molecular formula, and molecular weight?

What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH), hygroscopicity, melting points, and partition coefficient?

2.3.S.2 Manufacture

Who manufactures the drug substance?

How do the manufacturing processes and controls ensure consistent production of drug substance?

2.3.S.3 Characterization

How was the drug substance structure elucidated and characterized?

How were potential impurities identified and characterized?

2.3.S.4 Control of Drug Substance

What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

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?

2.3.S.5 Reference Standards

How were the primary reference standards certified?

2.3.S.6 Container Closure System

What container closure system is used for packaging and storage of the drug substance?

2.3.S.7 Stability

What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

2.3.P DRUG PRODUCT

2.3.P.1 Description and Composition

What are the components and composition of the final product? What is the function(s) of each excipient?

Does any excipient exceed the IIG limit for this route of administration?

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

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the Product

2.3.P.2.1.1 Drug Substance

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

2.3.P.2.1.2 Excipients

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

2.3.P.2.2 Drug Product

What attributes should the drug product possess?

How was the drug 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?

2.3.P.2.3 Manufacturing Process Development

(If the Product is a NTI Drug or a Non-Simple Dosage Form)

Why was the manufacturing process described in 2.3.P.3 selected for this drug product?

How are the manufacturing steps (unit operations) related to the drug product quality?

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

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

2.3.P.2.4 Container Closure System

What specific container closure attributes are necessary to ensure product performance?

2.3.P.3 Manufacture

(For All Products)

Who manufactures the drug product?

What are the unit operations in the drug product manufacturing process?

What is the reconciliation of the exhibit batch?

Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?

What are the in-process tests and controls that ensure each step is successful?

(If Product is Not a Solution)

What is the difference in size between commercial scale and exhibit batch? Does the equipment use the same design and operating principles?

(If the Product is a NTI Drug or a Non-Simple Dosage Form)

In the proposed scale-up plan what operating parameters will be adjusted to ensure the product meets all in-process and final product specifications?

What evidence supports the plan to scale up the process to commercial scale?

2.3.P.4 Control of Excipients

What are the specifications for the inactive ingredients and are they suitable for their intended function?

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?

2.3.P.6 Reference Standards and Materials

How were the primary reference standards certified?

2.3.P.7 Container Closure System

What container closure system(s) is proposed for packaging and storage of the drug product?

Has the container closure system been qualified as safe for use with this dosage form?

2.3.P.8 Stability

What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?

What drug product stability studies support the proposed shelf life and storage conditions?

What is the post-approval stability protocol?

Quality by Design Case Studies – the FDA CMC Pilot Program

Chi-wan Chen, Ph.D.
Office of New Drug Quality Assessment (ONDQA)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

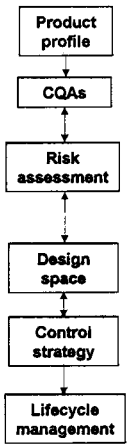
FIP Workshop on
Quality by Design and Quality Risk Management
Beijing, China
August 31, 2007

Outline

- CMC Pilot objectives and status
- QbD – a system approach
- Case studies
  - #1: Risk assessment and design space
  - #2: Real time release
  - #3: Drug substance CQAs
  - #4: Drug substance CQAs
- Summary of CMC Pilot
  - Risk assessment
  - Design space
  - Control strategy
  - Overall
- Next steps

2

QbD – a Systematic Approach



- Target the product profile
- Determine critical quality attributes (CQAs)
- Link raw material attributes and process parameters to CQAs and perform risk assessment
- Develop a design space
- Design and implement a control strategy
- Manage product lifecycle, including continual improvement

3

CMC Pilot Objectives and Status

- Objectives
  - To provide participating firms an opportunity to submit CMC information demonstrating application of QbD
  - To enable FDA to evaluate utility of CQOS and to implement new concepts (e.g., QbD, design space, real-time release) in Q8, Q9, and PAT Guidance
- Status
  - Program launched July 2005
  - 9 original and 2 supplemental NDAs accepted
  - 7 submitted to date: 5 approved, 1 approvable, 1 under review (as of June 11, 2007)
  - Others to be submitted within a year

4

Case Studies

The following case studies are based on select CMC Pilot NDAs and are presented with permission from the applicants

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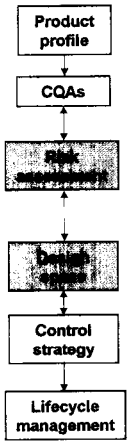
Case Study #1



Risk Assessment and Design Space

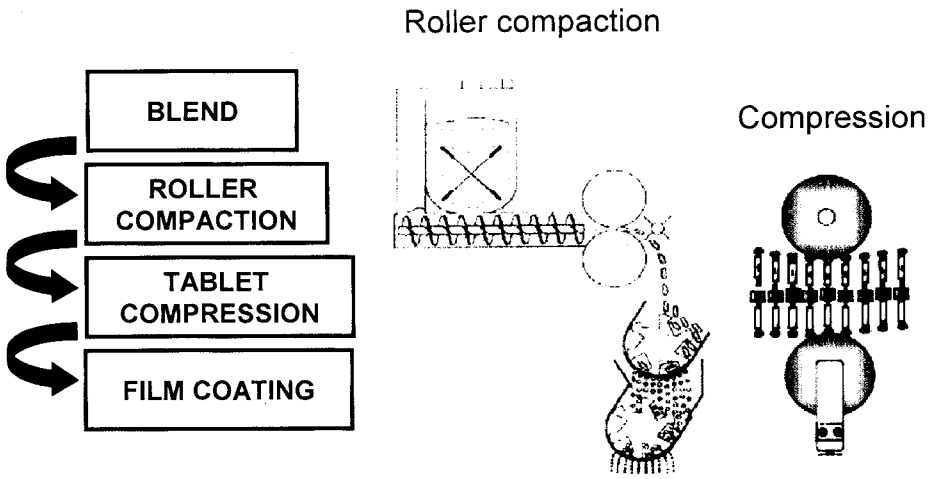
6

Product X

- Target product performance
  - Extended release formulation required for once-a-day dosing
    - Relatively high dose compound
    - High water solubility, moderate permeability
- Formulation
  - Controlled release using a polymer
  - Level-A IVIVC established

7

Manufacturing Process



Applying QbD

- Establish product critical quality attributes (CQAs)
  - Dissolution
  - Tablet hardness
- Link material attributes and process parameters to CQA
- Perform quality risk assessment
- Establish a design space
- Establish sound control strategy to ensure consistent product quality and performance

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Quality Risk Assessment

Failure Mode and Effect Analysis (FMEA)

Select process parameter / Quality Attribute	Polymer Concentration	API Particle Size	Roll Gap	PSD of Intra-granular Blend	Compressing Force	Weighted Average
Dissolution	10	1	1	1	1	10
Assay	3	5	7	1	1	9
Uniformity	1	5	7	4	1	7
Hardness	5	5	10	4	10	10
Yield	1	1	3	3	1	7
Rank	1	7	2	8	5	

Risk Prioritization

- Rating
  - Probability
  - Severity
  - Detectability
- Semi-quantitative values assigned using knowledge management
  - Multidisciplinary expert teams
  - Prior knowledge
  - Development experiments

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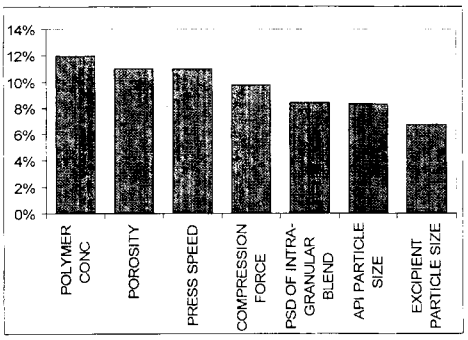
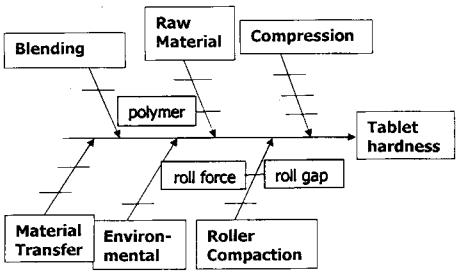
Risk Analysis to Identify CQA, CPP

Pareto Analysis



Relative importance of inputs based on FMEA

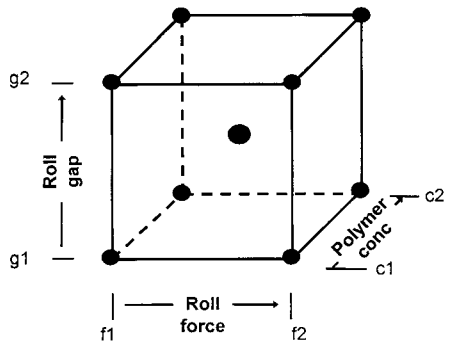
Ishikawa Diagram for Tablet Hardness



Identify critical input/process variables

Establishing Design Space

Design of Experiments (DOE)



DOE: Efficient method to evaluate the impact of input variables and process parameters (on product CQAs) and their interactions (not just correlations)

Critical input variables/process parameter:

- Polymer concentration
- Roll gap
- Roll force

Intermediate attributes:

- Porosity
- Compressibility

CQAs:

- Dissolution
- Hardness

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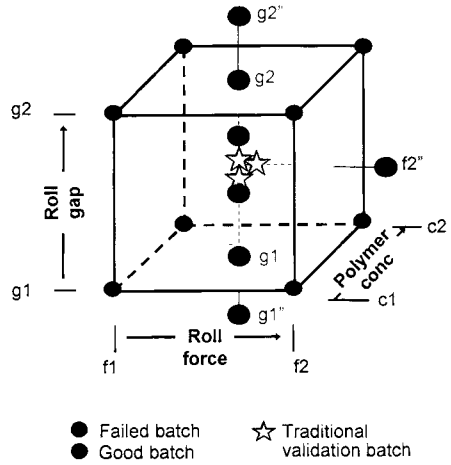
Confirming Design Space



- Design space for roller compaction predicted based on pilot scale is confirmed with production scale batches
- Production scale batches outside the design space failed tablet compression

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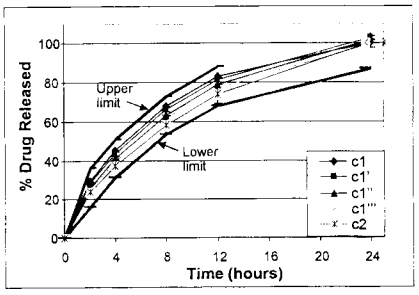
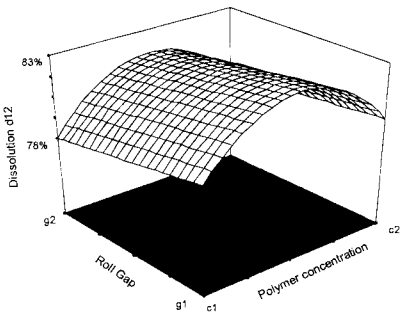
Establishing Design Space (cont'd)

Effect of Polymer Concentration on Dissolution



Typical 2-dimensional analysis

Interaction Effect of Roll Gap and Polymer Concentration on Dissolution



Z: Dissolution – d12
X: Polymer concentration
Y: Roll gap
Roll force fixed at f bar

Impact of Polymer Attributes on Performance – DOE Results

- Dissolution rate is dependent on polymer concentration
- Dissolution rate is largely independent (in the ranges studied) of
  - Roll force, roll gap, compression force
  - Polymer viscosity, particle size, substitutions
  - API particle size distribution
  - Tablet hardness
- Formulation performance is robust and resistant to variability in excipient and API inputs
- Design space established for polymer, API, compaction, compression

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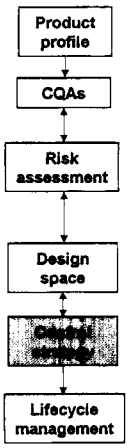
QbD vs. Traditional Approach – a simplified comparison

Aspect	Product X With QbD	Traditional
Product Quality Attributes	▪ Dissolution ▪ Tablet hardness	▪ Dissolution
Excipients	▪ Effect of polymer physical and chemical attributes understood ▪ Design space established	▪ Effect of polymer attributes unknown ▪ Reliance on USP spec
Manufacturing Process	▪ Process understood ▪ Design space established ▪ Process robust and adjustable	▪ Process not understood ▪ Operating ranges based on validation, focusing on repeatability ▪ Process changes at risk and fixed
Control Strategy	▪ Comprehensive, inc. control of input and process variability ▪ Predictive	▪ Limited, relying on end-product testing ▪ Reactive

Case Study #2



Control Strategy – Real Time Release

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Product Y

- Target product performance
  - Immediate release tablet
  - High water solubility, moderate permeability
- Formulation
  - Simple formulation
  - Common blend for all strengths

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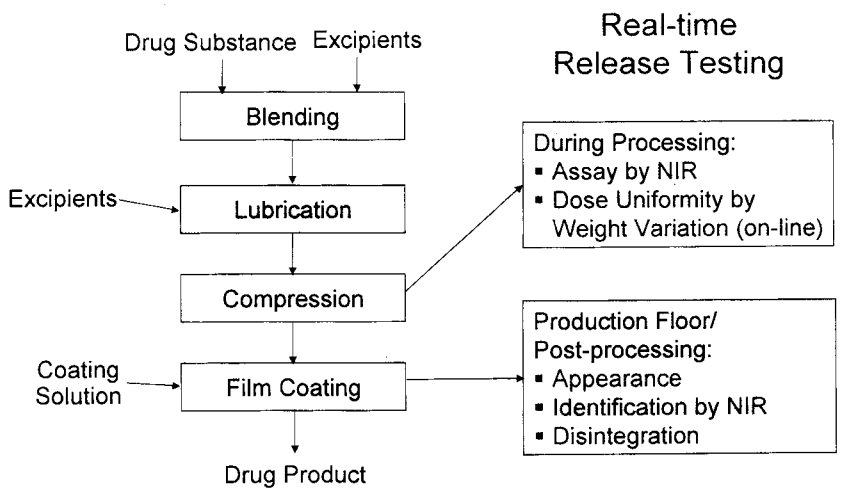
Drug Product Manufacturing



Traditional Release Testing

- Laboratory testing performed on samples after processing is complete
- Limited sampling
  - Very few samples taken
  - Samples may not adequately represent entire batch
- No opportunities to fix problems
  - Pass/Fail decisions only
  - Little information for fault diagnosis

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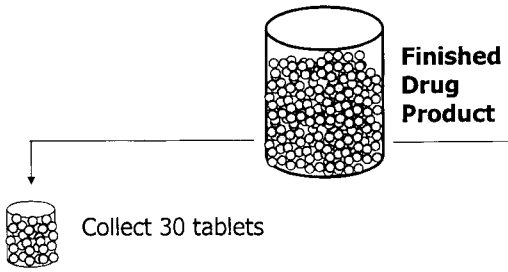
Traditional Release Testing



Content Uniformity (USP <905>)

STAGE 1
- Assay 10 tablets (typically by HPLC)
- PASS if all within 85-115% label claim and RSD ≤ 6.0%

STAGE 2
- Assay all 30 tablets
- PASS if all within 75-125% label claim and 29/30 within 85-115% label claim and RSD ≤ 7.8%

Assay
- Assay composite of tablets
- PASS if meets acceptance criteria

QbD for Real Time Release

- Real-time release is when all quality test results are obtained on-line/at-line during or immediately after manufacturing
- Manufacturing flexibility
  - Increased manufacturing efficiency
  - Measure and control in real-time
  - Adjust process to respond to variable inputs
- Increased assurance of quality
  - Science based release criteria
  - More representative of process
  - Greater process knowledge gained
- A more modern approach to manufacturing

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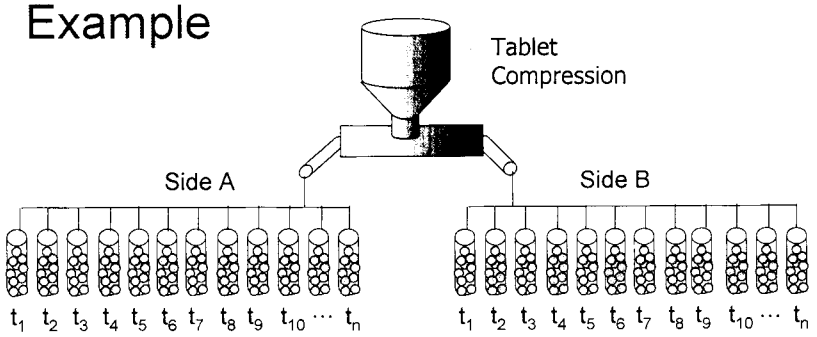
Real Time Release – Sampling Plan Example



Dose Uniformity:
- Stratified sampling during compression
- Automatic weight check on all sampled tablets
- Adjust press as needed
- Use non-parametric test criteria

Assay:
- Take several tablets from each vial at end of compression
- Assay using NIR

QbD vs. Traditional Approach to Specification – a Simplified Comparison

Specification	Product Y with QbD	Traditional
Identity	At-line NIR	Off-line
Assay	At-line NIR on uncoated tablet	Off-line HPLC of coated tablet
Disintegration/ dissolution	At-line disintegration	Off-line dissolution
Dose uniformity	On-line weight variation	Off-line content uniformity by HPLC

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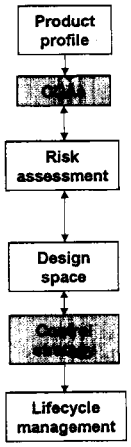
Case Study #3



Rational Approaches to Drug Substance CQAs – Particle Size Distribution – and Control Strategy

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Drug Substance M – Potential CQA's

Potential CQA	Free Base Formation	Final Crystallization	Final Drying
Assay	X		
Chiral Purity	X		
Impurity Content	X	X	
Metals Content	X	X	
Water Content		X	X
Residual solvent Content			X
Polymorphic Form		X	
Particle Size Distribution		X	

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Impact of Potential DS CQA's

Potential CQAs	Impact
Assay Impurity content Chiral purity Metals content Residual solvent	Efficacy and safety
Polymorphic form Water content	Dissolution & stability
Particle size distribution (PSD)	Processability

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Is PSD a CQA?

- Findings within PSD ranges studied:
  - No impact on dissolution
  - No impact on content uniformity
  - No impact on blending
  - Potential segregation post blend, based on prior knowledge and experience
  - Increased tablet sticking during compression with high levels of fines in DS

➡ **PSD is a potential CQA**

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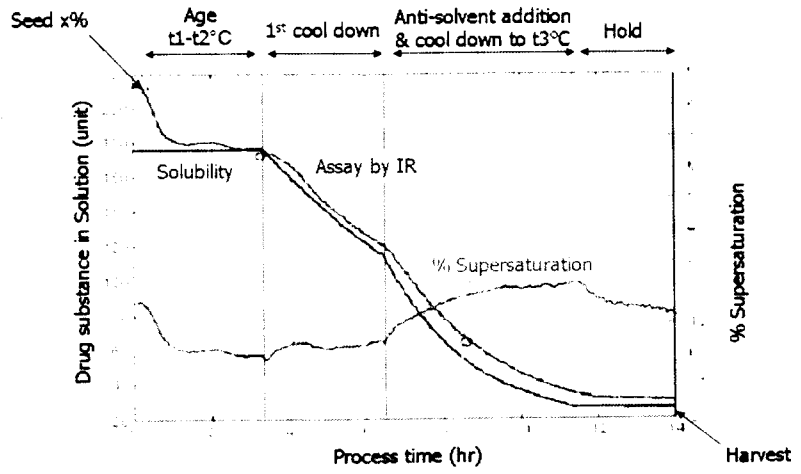
Particle Size Distribution Control



- Controlled crystallization with seeding
- Processing occurs entirely in thermodynamically favored regime

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Proposed Control Strategy

- Process control of crystallization step
- Inclusion of a broad range PSD in drug substance specification
  - Based on results from drug product process development experience
- Inclusion of a drug substance PSD control range in drug product control strategy
  - Based on demonstrated range
  - If PSD falls outside initial control range
    - Additional drug product and process evaluation will be conducted
    - Results may be used to update PSD specification

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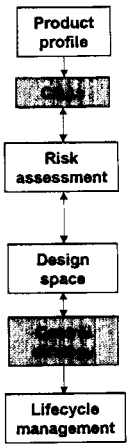
Case Study #4



Rational Approaches to Drug Substance CQAs – Toxic Impurities and Polymorphic Form – and Control Strategy

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Drug Substance N – Potential CQAs and Control Strategy

Potential CQAs	Control Strategy
Toxic process impurities	▪ Greater emphasis on contribution of manufacturing processes to quality control ▪ Move to upstream testing
Polymorphic form	Process capability = batch experience + design of experiments

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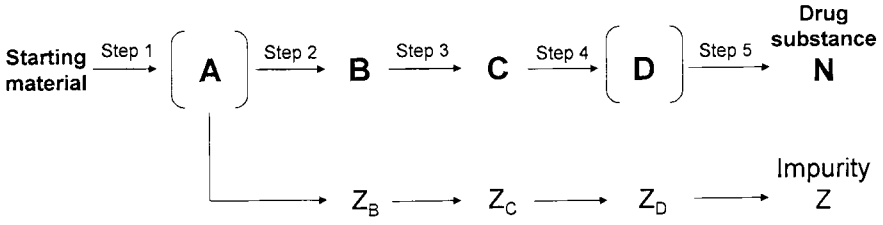
Understanding of Impurity Z



- Point of formation, and fate, of impurity Z and parameters affecting them were determined based on
  - Understanding of organic reactions
  - Spiking and purging studies
  - Data showing capability of downstream purification steps

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Rational Control Strategy for Impurity Z

- Process control of all steps
- Impurity test performed on intermediate C, not part of drug substance specification
  - Test closer to point of formation
  - Excellent detectability using sensitive analytical method
- Acceptance criterion for Z_C based on
  - Level deemed safe/qualified for the drug substance, not levels observed in intermediate C in routine manufacturing
  - Demonstrated capability of downstream purification steps

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Understanding and Controls of Polymorphism

- Justification for omitting polymorph testing from drug substance specification
  - Similar (high) solubility among polymorphic forms
  - Most stable form selected as drug substance
  - No conversion on stability (humidity challenges)
  - Batch experience
  - DoE to identify design space in final crystallization

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Summary of CMC Pilot

- Observations on the submissions to date
  - Risk assessment
  - Design space
  - Control strategy
  - Overall

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Risk Assessment

- What are good?
  - Limited risk assessment, inc. FMEA
- What could be improved?
  - Summary of prior experience when cited
  - Systematic risk analysis of how raw materials, process steps, and process parameters affect product quality
  - Discussion of comprehensive control strategy that reduces risks to product quality
  - Discussion of controls in place to reduce potential risks to product quality upon process changes inside or outside the design space

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Design Space

- What was observed to date?
  - Most applications included a design space for DP; only some for drug substance (DS)
  - Most design spaces for process parameters; only some included formulation components (excipients, DS)
  - Methods for determining design space included
    - One variable at a time experiments
    - Statistically designed experiments (DOE's)
    - Modeling approaches

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Design Space (cont'd)

- What could be improved?
  - Effect of formulation component properties on process performance and product quality studies
  - Multivariate interactions examined
  - Supportive mathematical models utilized as appropriate
  - Scale-up and equipment issues considered
  - Effect of operation or site change considered
  - Uncertainty addressed with risk analysis

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Control Strategy

- What are good? Examples:
  - Certain tests for drug substance CQAs moved upstream to where the control points are
  - On-line analyzers (non-PAT) for intermediates
  - In-process testing (in lieu of end-product testing) for
    - Identification and assay using at-line NIR
    - Dose uniformity by at-line weight variation
  - Real-time release using PAT
- What could be improved?
  - Better utilization of knowledge in setting specs
  - Better understanding of excipient properties, instead of relying solely on compendial standards
  - More meaningful sampling for drug product testing
  - Experience in setting real-time release specs

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Overall Observations

- More scientific information was shared
- Risk assessments, though limited, were performed
- Design spaces were proposed
- Various flexible regulatory approaches were explored
- Risk-based regulatory decisions were enabled
- Pilot benefited FDA and industry in implementing QbD
- Learning from Pilot is being input into ICH Q8 revision
- Challenges remain for industry and FDA

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Next Steps

- Sharing lessons learned from CMC Pilot
  - With each applicant under the Pilot
  - With other disciplines, including Compliance and Field investigator, in FDA
  - With industry in future public forums
  - With regulatory agencies in other regions
- Facilitating QbD submissions outside CMC Pilot
- Evaluating need for training and new guidances (FDA and ICH)

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