Development & The US FDA Approval of Generic Drugs

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Agenda

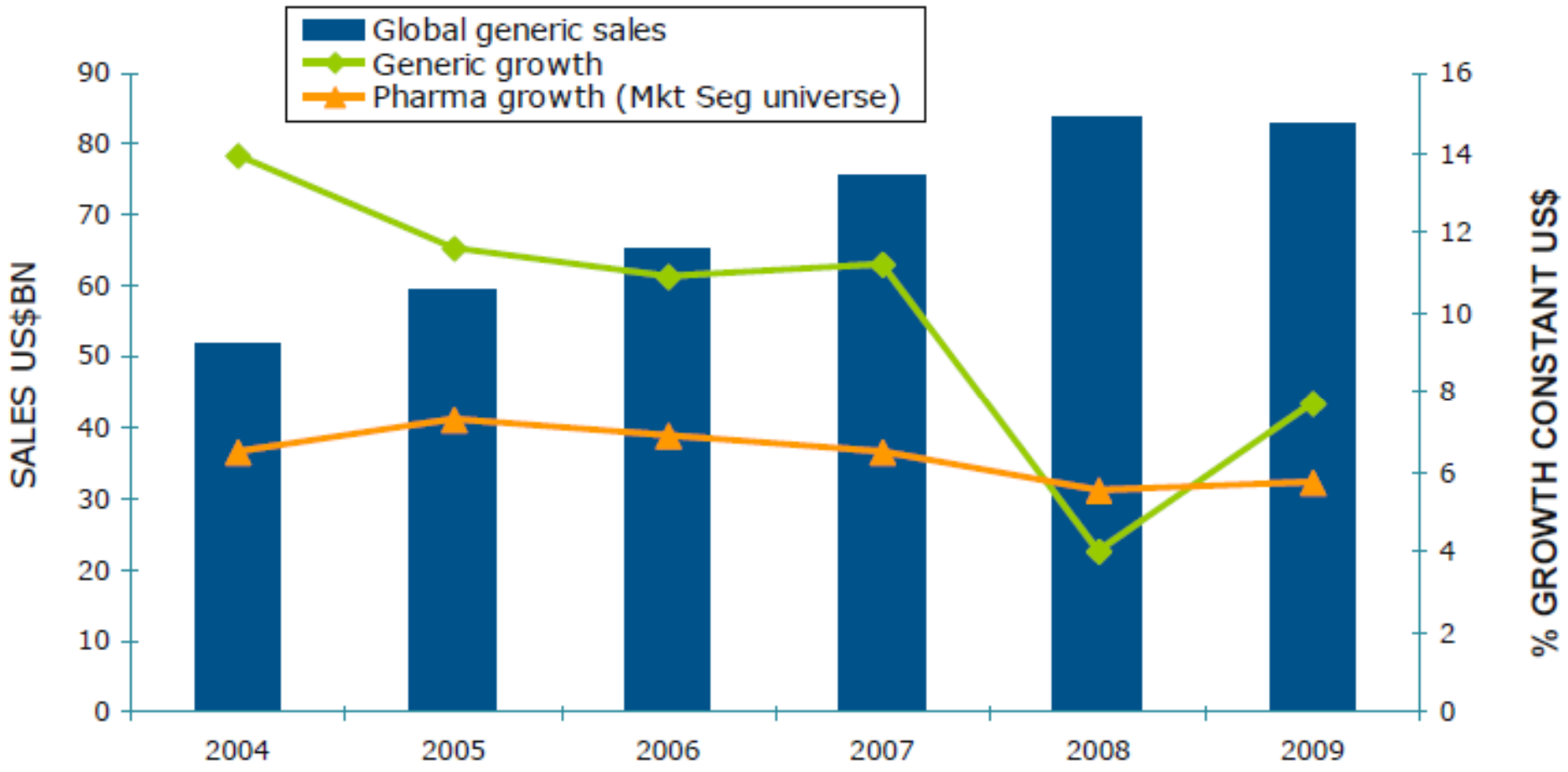
- About Generic Drugs
- Business Strategy for Generic Drugs
- Generic Drug Product Development
- Generic Drug Approval Process
- Question-Based Review
- Summary

What are Generic Drugs

US FDA's Definition:

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.

Generic Share of Market



Source: IMS Health, MIDAS, Market Segmentation, MAT Sep 2009, Rx only

The global generics market reaches $8.3bn while growth recovers climbing to 7.7%.

Generic Pharma in U.S.

- **Generic Prescriptions**
  - Generic medicines account for 69% of all prescriptions dispensed in the United States, yet only 16% of all dollars spent on prescriptions. (source: IMS Health)
  - Generic pharmaceutical products are used to fill nearly 2.6 billion prescriptions every year.

Drug Price Competition and Patent Term Restoration Act of 1984 – Waxman-Hatch Act

- Created a framework for patent term extensions and nonpatent exclusivity periods for brand name drug products
- Created an *Abbreviated* mechanism for approval of generic copies of all drugs originally approved after 1962, by stating that pre-clinical and clinical testing does not have to be repeated for generics.
- Provided for pre-patent expiration testing (Bolar provision) and generic drug exclusivity

What are the Basic Requirements?

- Contain the same API as the innovator drug (inactive ingredient may vary)
- Be identical in strength, dosage form, and route of administration to RLD
- Have the same use indications as RLD
- be bioequivalent to RLD
- meet the same batch requirements for identity, strength, purity and quality
- be manufactured under the same strict standards of FDA's GMP regulations required for innovator products

Basic Requirements for a Generic Drug

- Regulatory & Legal
- Labeling
- CM&C/Microbiology
- Bioequivalence

When can a Generic Drug be Marketed?

Regulatory & Legal Requirements:

- After patent & exclusivity protection ends, or
- Patent owner waives its rights, and
- FDA requirements are met.

Regulatory & Legal Requirements

➢ Orange Book:

- Approved Drug Products with Therapeutic Equivalence Evaluations
- List of drug products approved on the basis of safety and effectiveness by the US FDA under the Federal Food, Drug, and Cosmetic Act.

➢ Patents:

- All approved patent numbers and expiration dates
- Patents that claim the active ingredients or ingredients
- Drug product patents which include formulation/composition patents
- Use patents for a particular approved indication or method of using the product

➢ Code (Two-Letter) for Existing Generics:

- First letter: if it is bioequivalent; Second letter: Additional information, e.g., dosage forms
- Equivalence rating to the innovator product;
- If the first letter is **A**, no biostudy needed for approval (i.e. AA, AN, AO, AP, AT-no problem, AB-demonstrated) - substitutable
- If the first letter is B, **NOT to be therapeutically equivalent** to other products **(BC, BD, BE, BN, BP, BR, BS, BT, BX, B*).**

Regulatory & Legal Requirements

A Certification from ANDA sponsor:

- Paragraph I: that such patent information has not been filed;
- Paragraph II: that such patent has expired;
- Paragraph III: of the date on which such patent will expire, or

A Certification from ANDA sponsor:

- Paragraph IV: that such patent is invalid or will not be infringed by the manufacturer, use, or sale of the new drug for which the application is submitted.

- Challenge the listing of the patent;
- File a statement that the application for use is not claimed in the listed patent;
- **MUST** notify the patent holder of the submission of the ANDA. If the patent hold files an infringement suit within **45** days of the ANDA notification, FDA approval for the generic drug is automatically postponed for **30** months.

Product Insert Label

- **“Same” as brand name labeling**
- **May delete portions of labeling protected by patent or exclusivity**
- **May differ in excipients, PK data and how supplied**
- **Should use the newest version available**
- **Should use the label from FDA website <drugs@FDA>, rather than DailyMed**

Side-by-side comparison is required! Sponsor’s label in SPL format may be provided.

Chemistry, Manufacture & Control

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

CM&C: Product Development

1. Decide what product to pursue
2. Find source of API (DMF w/US FDA), excipients & packaging materials
3. Develop a unit formula
4. Develop manufacturing process and scale up
5. Develop, verify and validate analytical methods
6. Set product specification-Control Strategy
7. Manufacture submission batches
8. Conduct BE study or waive BE study
9. Prepare CTD/eCTD and file with US FDA

What are difference in 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 & Release	5. Testing & Release
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

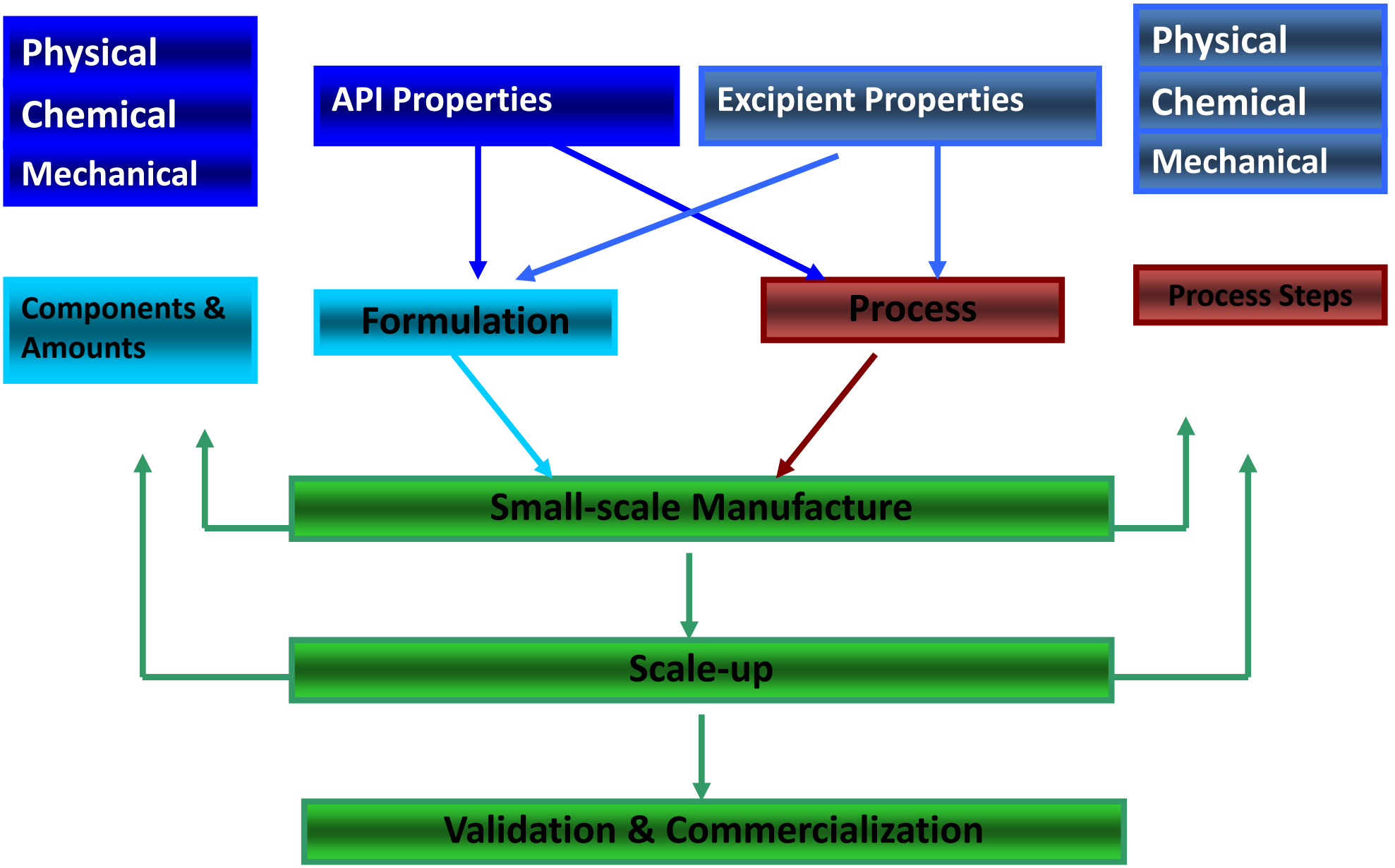
What are difference in NDA vs. ANDA Review Process?

NDA Requirements	ANDA Requirements
Stability data	**Stability data**
Three batches	One batch
6 M Accelerated	3 M Accelerated and
12 M Storage	Long-term storage commitment
Approval Time	**Approval Time**
6 M for priority	6 M cycle*
12 M for standard**	

*Median approval times for original ANDA is 18.3 months, 17.3 months and 16.3 months for years of 2002, 2003 and 2004 respectively.

**User fee: 1.5MM.

Develop A Drug Product



CM&C: Quality by Design

The short version…

QbD is a systematic, science-driven, knowledge and risk based approach to developing, manufacturing and controlling pharmaceutical products throughout their lifecycle.

CM&C: Quality by Design

Product & process design and development

Define desired product performance upfront; identify product CQAs

→

Design formulation and process to meet product CQAs

↕

Understand impact of material attributes and process parameters on product CQAs

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Identify and control sources of variability in material and process

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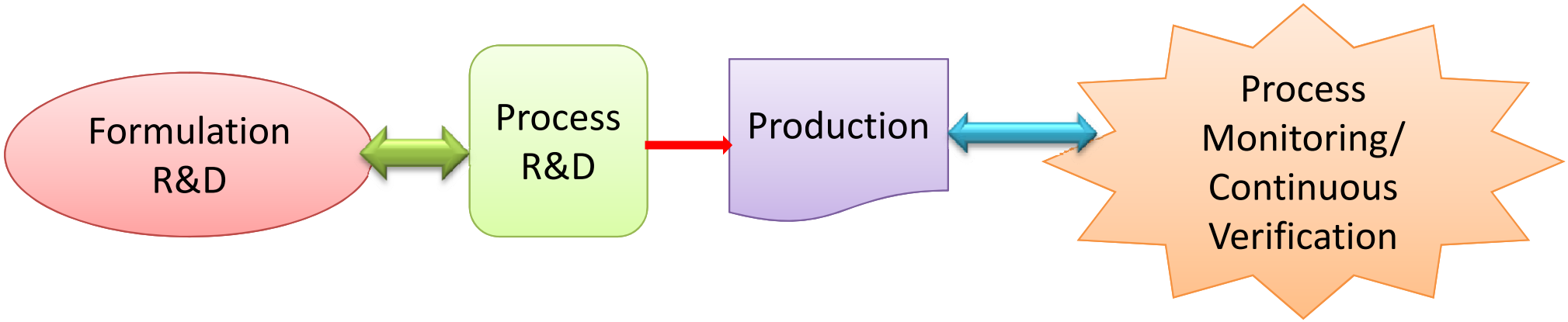
Continually monitor and update process to assure consistent quality

Risk assessment and risk control

CM&C: Linkage between Q8, Q9 & Q10



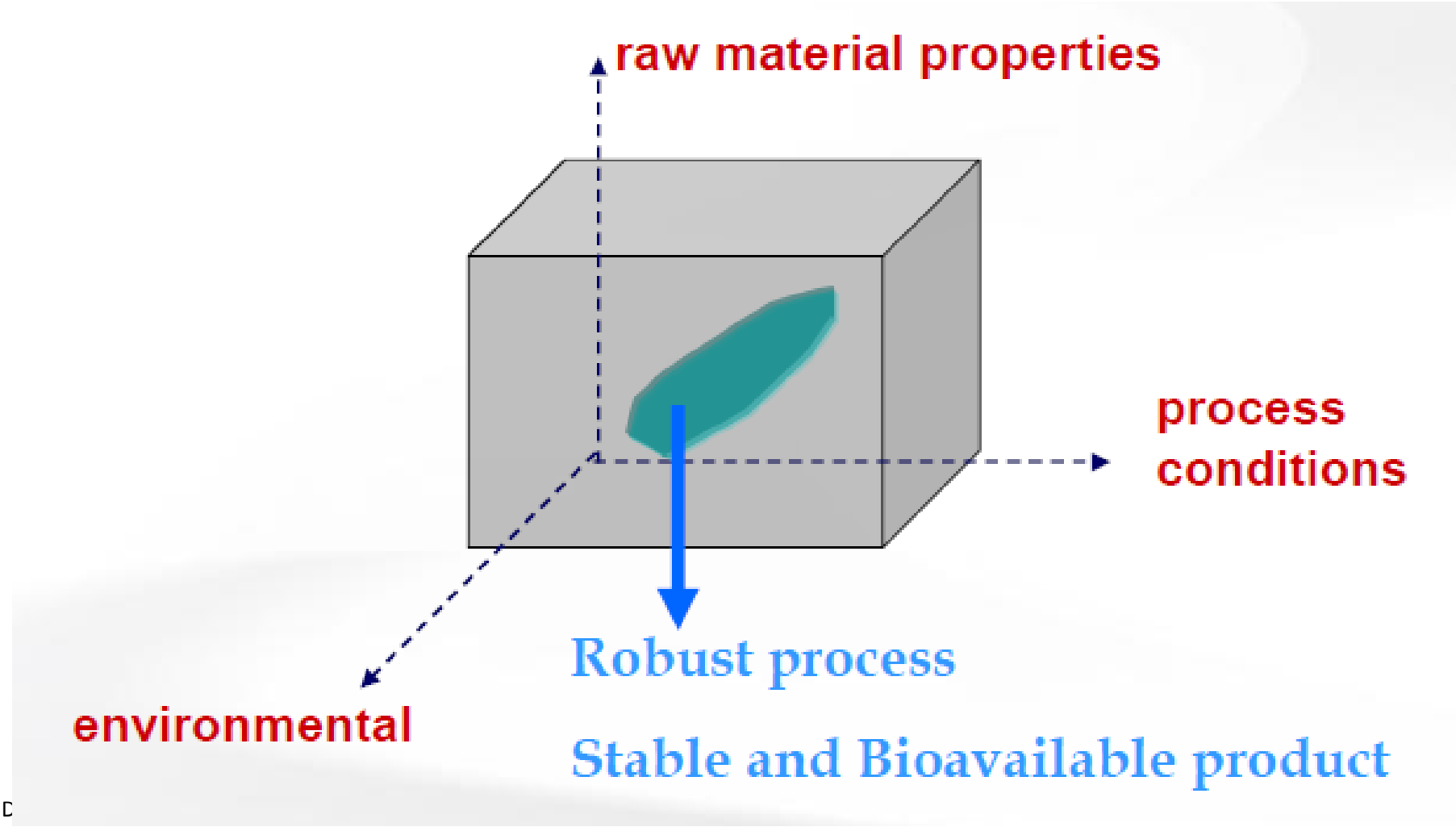
ICH Q8(R) Pharmaceutical Dev

ICH Q9 Quality Risk Mngmnt

ICH Q10 Pharmaceutical Quality System

QbD: Design Space

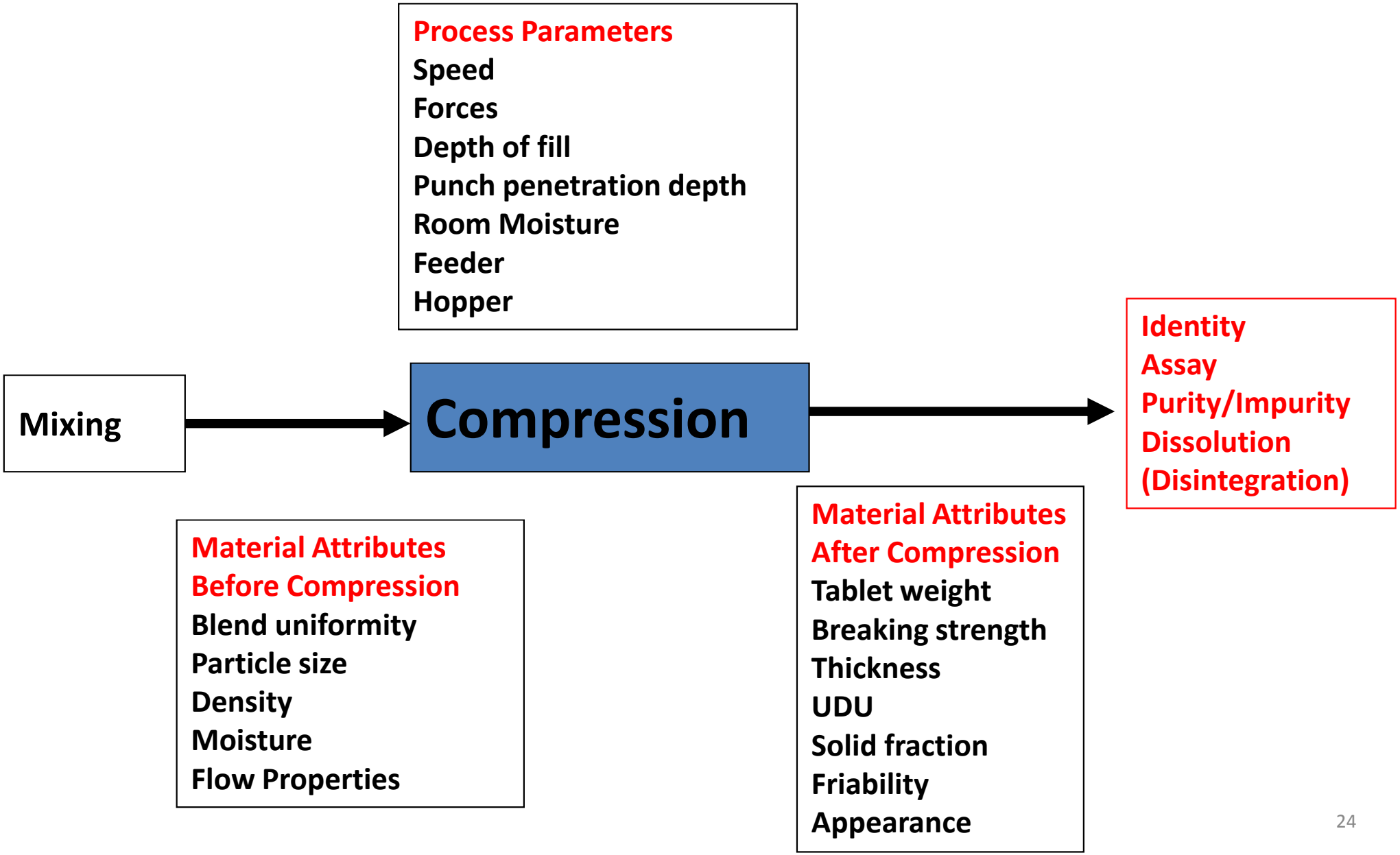
Multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters demonstrated to provide assurance of quality



QbD: CMA & CPP

- ➢Critical Material Attribute (CMA)
  - A physical, chemical, biological or microbiological property or characteristic of a material that should be within an appropriate limit, range, or distribution to ensure the desired product quality
- ➢Critical Process Parameter (CPP)
  - A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

CMAs and CPPs: an Example



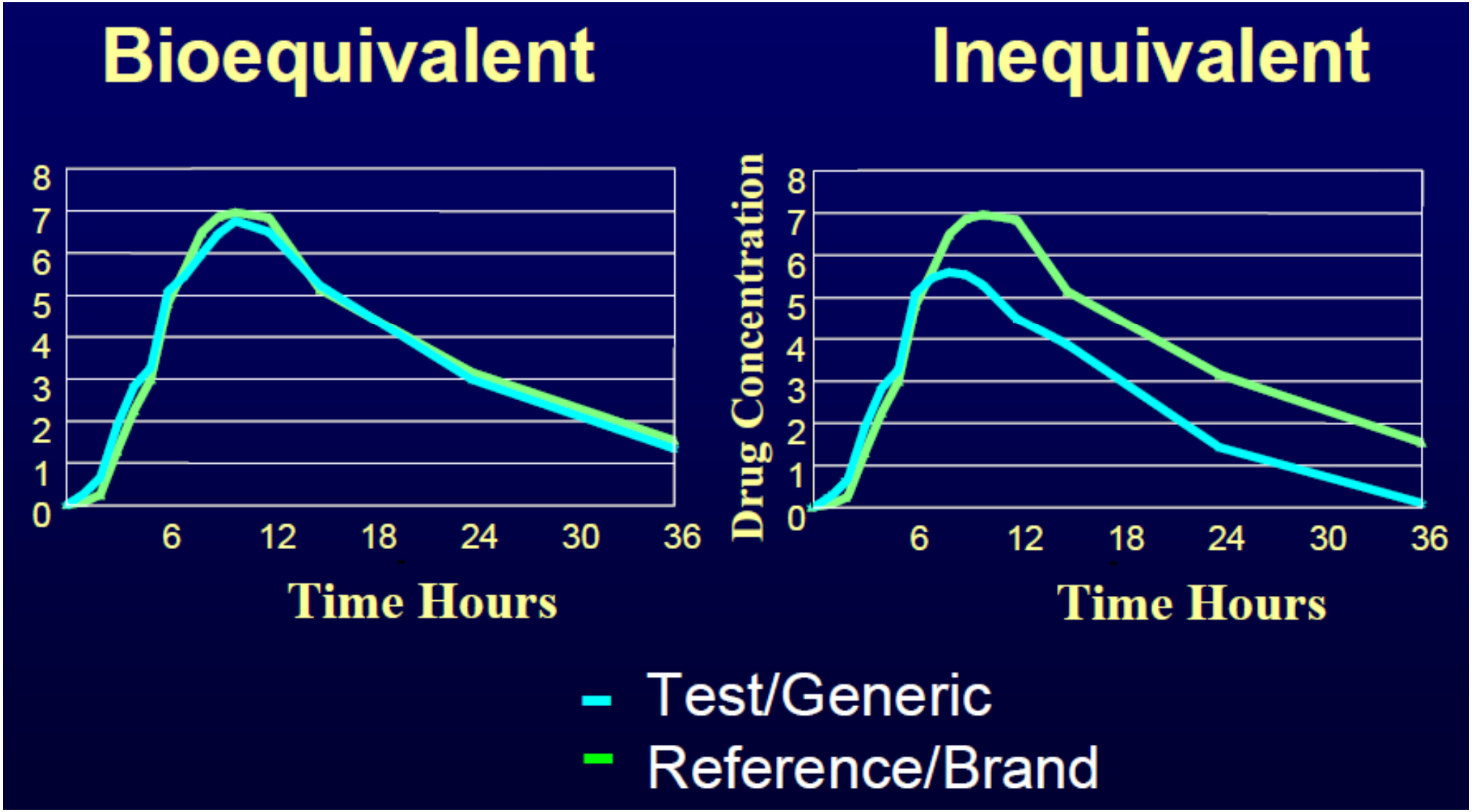
Bioequivalence

A generic drug is considered to be bioequivalent to the RLD if:

- the rate and extent of absorption *do not* show a significant difference from the listed drug, or

- the extent of absorption *does not* show a significant difference and any difference in rate is intentional or *not* medically significant

What is Bioequivalence?



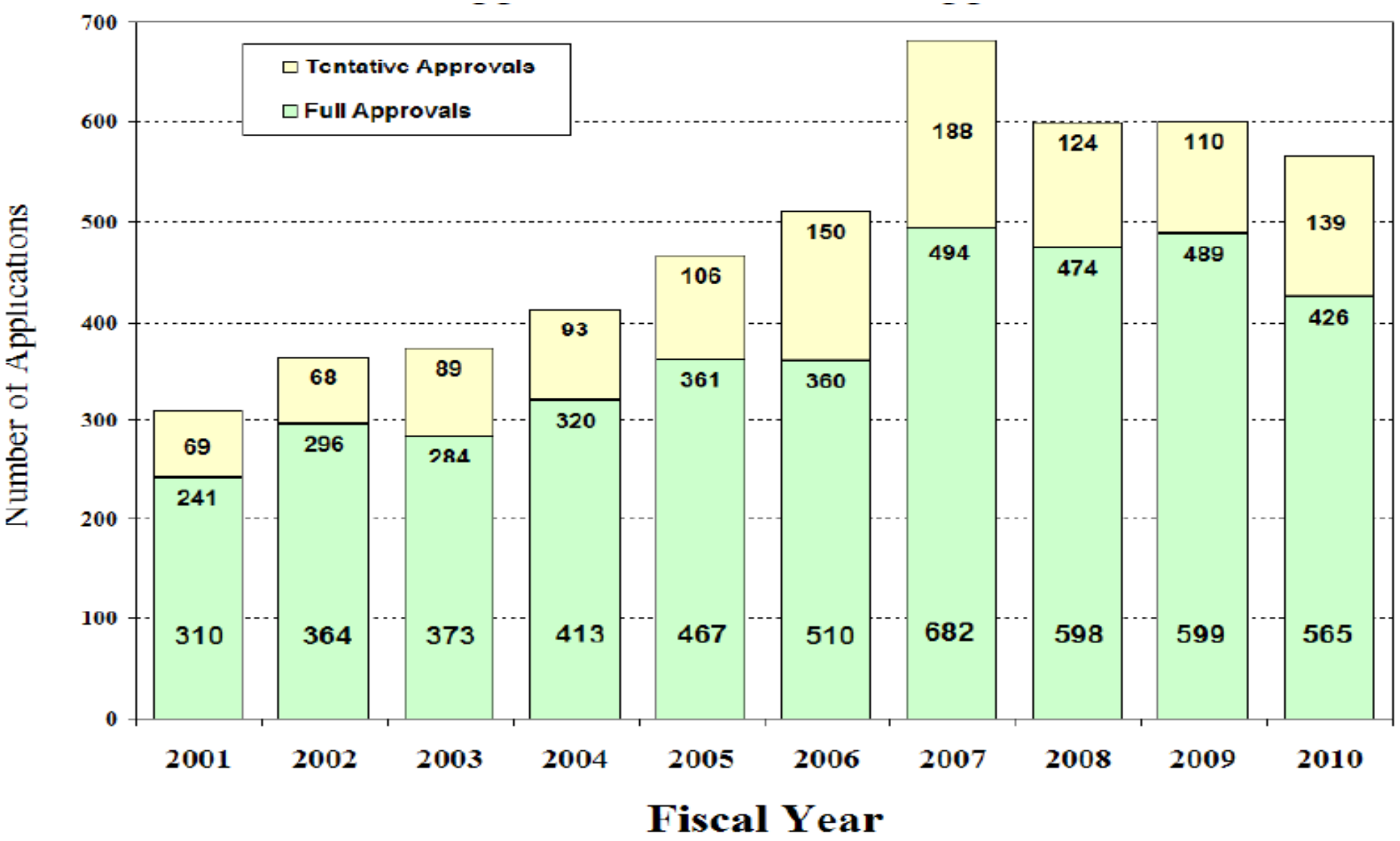
Bioequivalence Criteria
(Two One-sided Tests Procedure)

- AUC and Cmax
  - 90% Confidence Intervals (CI) must fit between 80%-125%
  - Test (T) is not significantly less than reference
  - Reference (R) is not significantly less than test
  - Significant difference is 20% (α = 0.05 significance level)
    - T/R = 80/100 = 80%
    - R/T = 80% (all data expressed as T/R so this becomes 100/80 = 125%)

Waivers of In Vivo Study Requirements

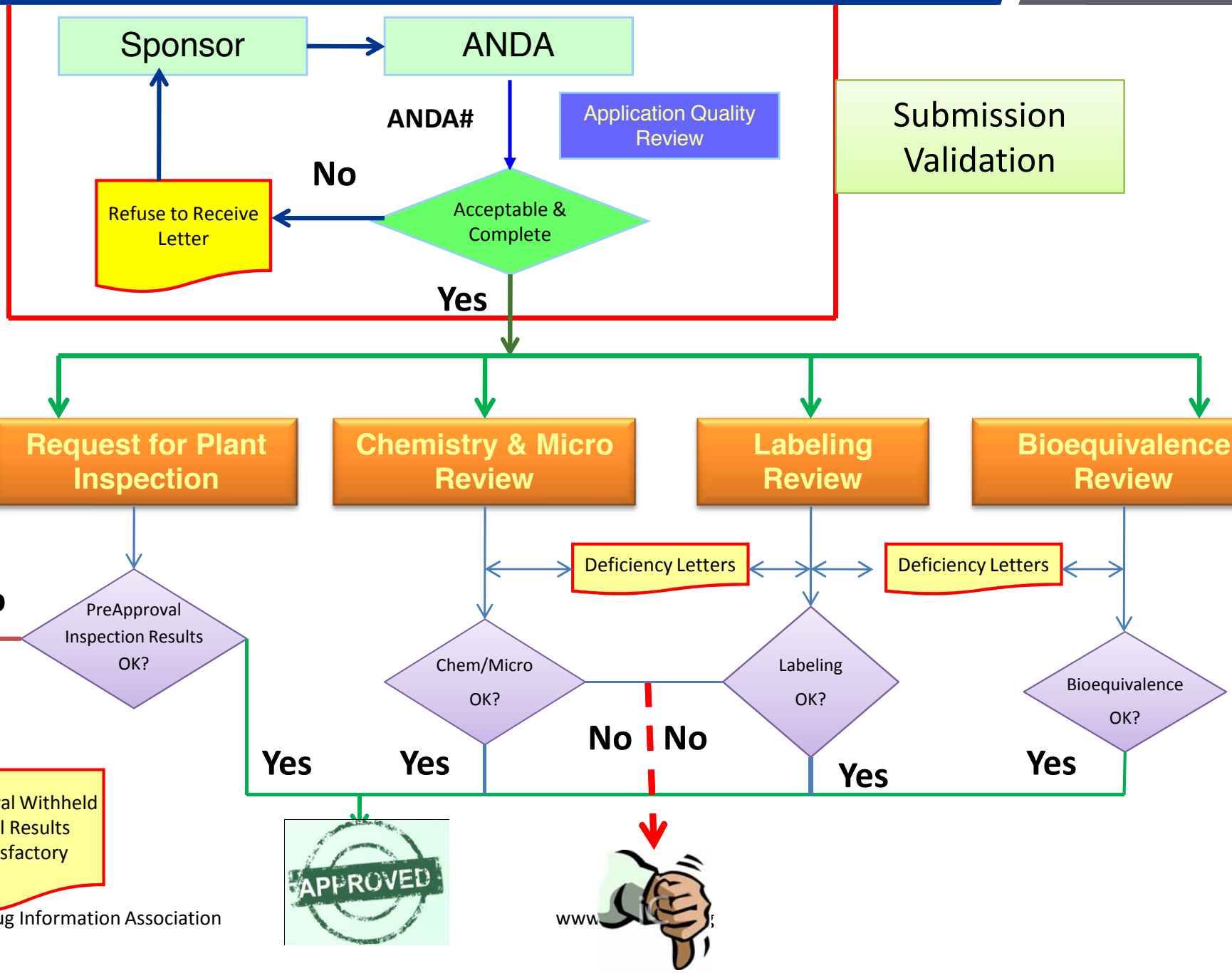
- Criteria (21 CFR 320.22)
  - In vivo bioequivalence is self-evident
  - Parenteral solutions
  - Inhalational anesthetics
  - Topical (skin) solution
  - Oral solution
  - Different proportional strength of product with demonstrated BE

ANDA Approvals



Source: FDA in GPhA Annual Technical Meeting 2010

Generic Drug Review Process



ANDA: Question-based Review

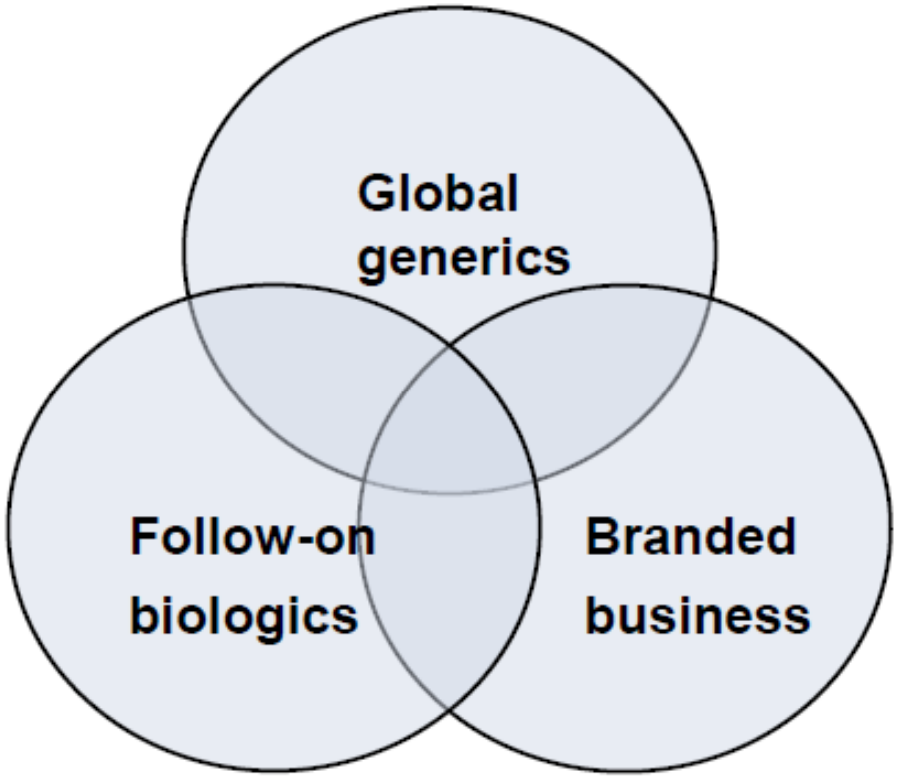
- **Question-based Review (QbR) is a general framework for a science and risk-based assessment of product quality**
- **QbR contains the important scientific and regulatory review questions**
- **ANDA sponsors answer the questions**
- **OGD reviewers evaluate the responses to the questions**

Advantages of QbR

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

Future Generic Industry

- Strong Management
- Control manufacture cost
- Globalization
- Diversified product pipeline
- Biologics- vague and expensive



Summary

- Generic industry has been well established and strictly regulated in the US.
- The bar to enter the circle becomes higher in terms of product quality & GPM compliance.
- Question-based Review has been used by FDA for generic drug approval & will be required soon.
- Generic drug development is a good opportunity for China Pharma to enter global pharmaceutical competition.

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