

Generic Drug Product Quality Assessment

Robert Berendt, PhD

Branch Chief

Office of Lifecycle Drug Products

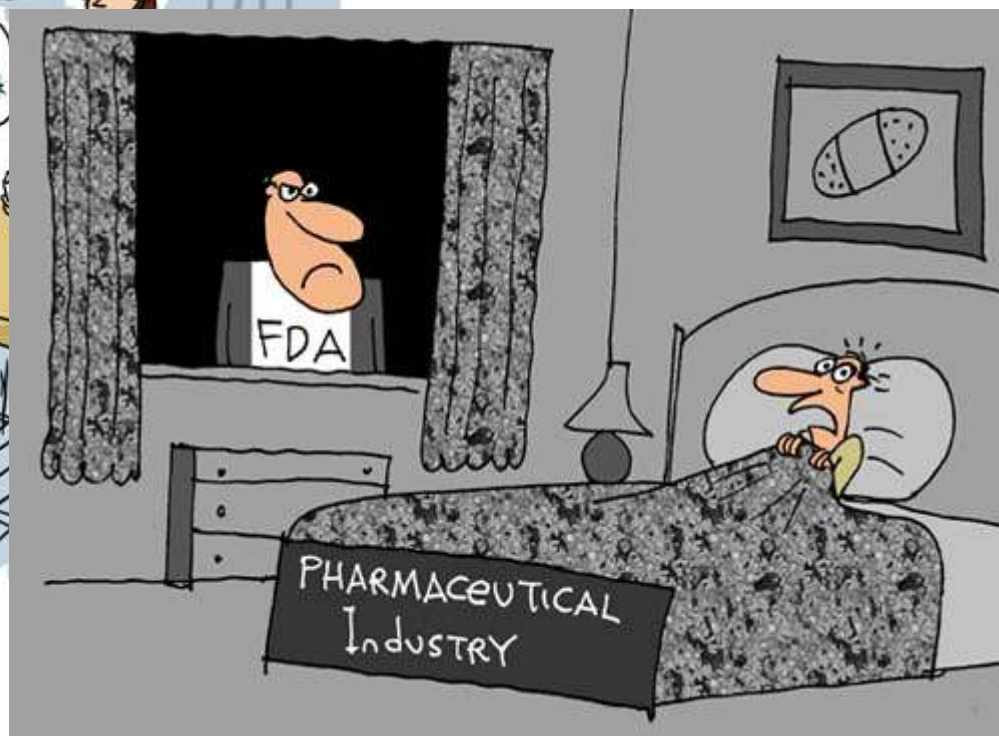
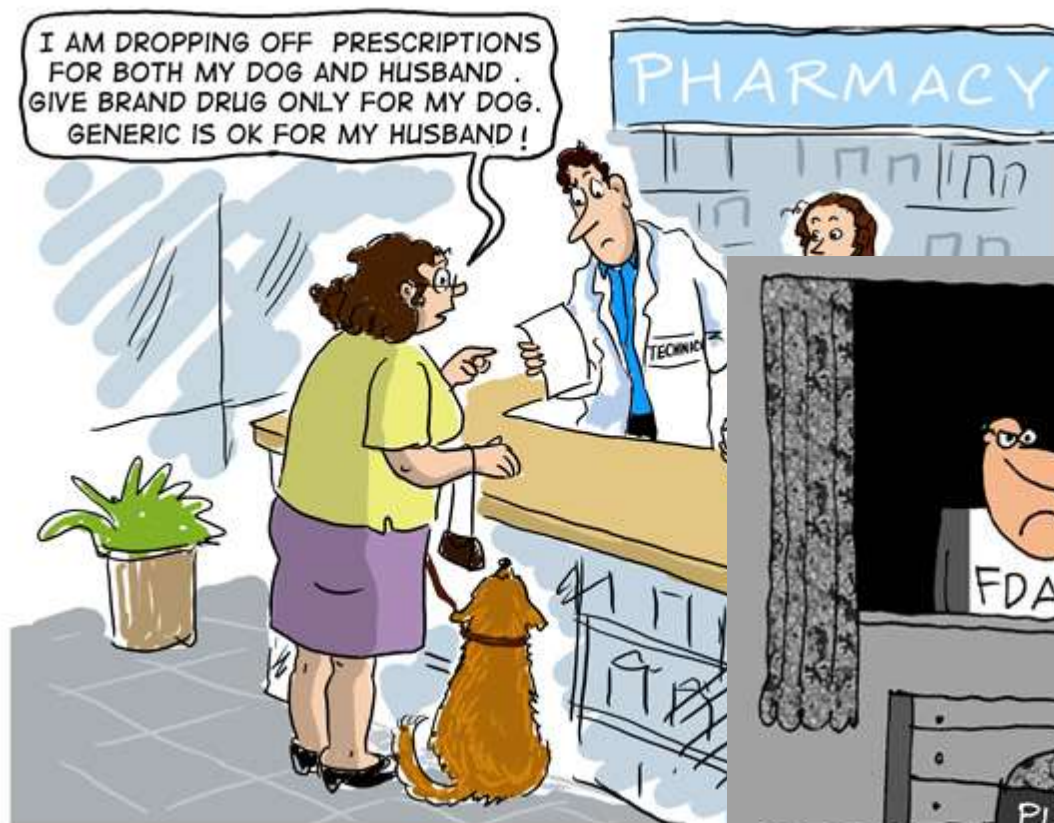
Office of Pharmaceutical Quality

CDER/FDA

Generic Drug Forum

April 12, 2018

Generic Drug Product Quality



Overview

- Team-based quality assessment
- Key considerations
- Drug product quality assessment
 - Drug substance
 - Drug product
 - Labeling
- Major deficiencies
- Take-away message

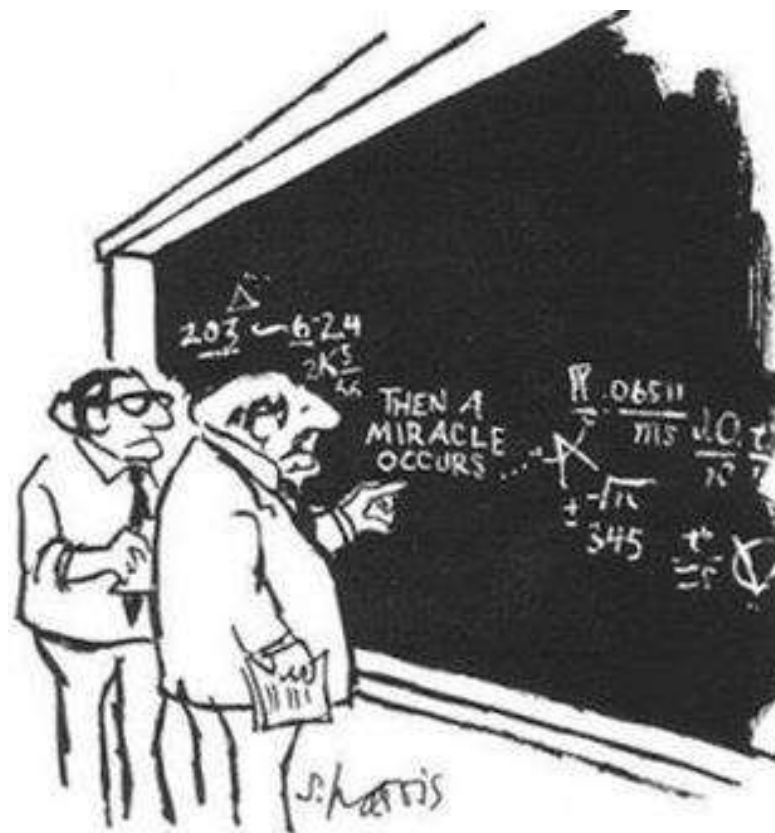
ANDA Quality Assessment (Team-Based)

- | | |
|--------------------|---|
| • Drug Substance* | Office of Lifecycle Drug Products
(OLDP)
Drug Product Quality Assessment |
| • Drug Product | |
| • Labeling | |
| • Process | Office of Process and Facilities
(OPF) |
| • Facilities | |
| • Microbiology | |
| • Biopharmaceutics | Office of New Drug Products
(ONDP)* |

*Review of Drug Substance also involves ONDP's Division of Lifecycle API

Key Considerations: Your application should...

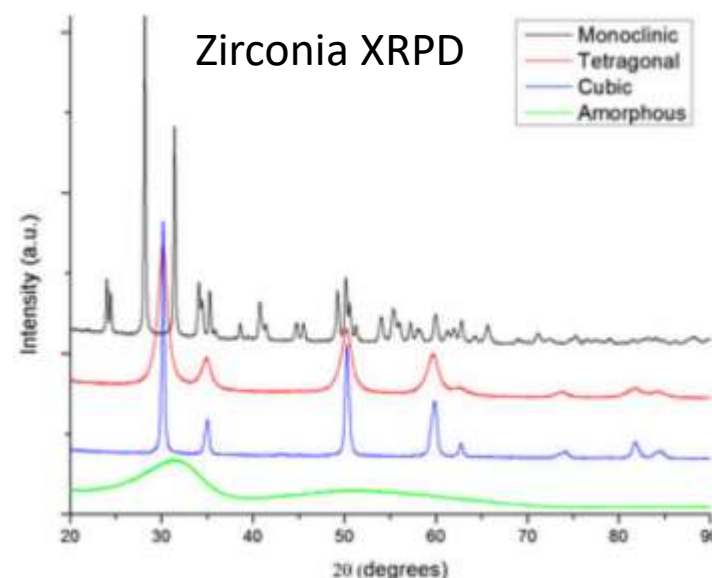
- ★ Meet all regulatory requirements
- ★ Demonstrate product understanding (CQAs)
- ★ Mitigate risks
- ★ Provide supporting data



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

Drug Substance

- Typical drug substance CQAs
 - Polymorphism
 - Particle size
 - Solubility (pH dependence)
 - Chemical stability
- Differences among suppliers
- Risks to drug product quality
 - Solution for injection?
 - Modified-release tablet?



DOI: 10.1111/jace.13504

Product Design and Formulation

- Design and formulation differences from innovator product (RLD)
 - May be allowed (21 CFR 314.94)
 - But may increase risk
- Demonstrate that differences do not affect safety
- Consider size, shape, and visual differences
- Consider patient and administration



Control of Excipients

- USP-NF monograph testing = minimum requirement
- Communicate with the supplier to ensure understanding of your raw materials
- Additional control strategies/tests may be warranted
 - Particle size distribution
 - Polymer viscosity range
 - BSE/TSE
 - Melamine contamination
 - Impurities

Control of Drug Product

- Finished product testing alone should not be relied upon to ensure quality
- Impurities
 - Refer to MAPP 5017.2 and ICH guidance (ICH Q3A-Q3D, M7)
 - Caution: Submission of pharm/tox data in an amendment may significantly alter the assessment timeline
- Analytical methods
 - Provide the standard test procedure (STP) for all testing
 - Provide validation/verification/transfer reports
 - Referencing compendia or DMF alone is insufficient
- Assay – drug substance and critical excipients

Container Closure System

- Appropriate to ensure quality over proposed shelf life?
- Safety, function, performance, compatibility
 - Chemical stability? (oxygen scavengers, desiccant, nitrogen gas, etc.)
 - Physical stability? (desiccant, structural protection, etc.)
 - Compatibility and protection from contamination (glass delamination, extractable/leachable assessment, etc.)
 - Consider in-use stability issues that may require additional data

Container Closure System



Finished Product Stability

- Poor stability often a result of lack of product understanding
- Accelerated and long-term (6 months at filing)
- Photostability
- In-use stability
- Test results per final specification to support the shelf life
 - Examples of missing testing/results
 - Physical stability (polymorphism, phase changes)
 - In vitro release testing (dissolution)

Labeling

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING – LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS

1 INDICATIONS AND USAGE

- 1.1 Thrombotic Stroke
- 1.2 Coronary Stenting

2 DOSAGE AND ADMINISTRATION

- 2.1 Thrombotic Stroke
- 2.2 Coronary Stenting
- 2.3 Renally Impaired Patients

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hematological Adverse Reactions
- 5.2 Monitoring for Hematological Adverse Reactions
- 5.3 Anticoagulant Drugs
- 5.4 Bleeding Precautions
- 5.5 Monitoring: Liver Function Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Studies Experience
- 6.2 Postmarketing Experience

7 DRUG INTERACTIONS

- 7.1 Anticoagulant Drugs
- 7.2 Phenytoin
- 7.3 Antipyrine and Other Drugs Metabolized Hepatically
- 7.4 Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs
- 7.5 Cimetidine
- 7.6 Theophylline
- 7.7 Propranolol
- 7.8 Antacids
- 7.9 Digoxin
- 7.10 Phenobarbital
- 7.11 Other Concomitant Drug Therapy
- 7.12 Food Interaction

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment
- 8.7 Hepatic Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

- 14.1 Thrombotic Stroke
- 14.2 Coronary Stenting

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

- 17.1 Importance of Monitoring
- 17.2 Bleeding
- 17.3 Hematological Adverse Reactions
- 17.4 FDA-Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

Major Deficiencies – Drug Product Quality

(list not comprehensive)

- Missing toxicological studies to qualify an unqualified impurity
- Unacceptable physical properties for drug product
- Need full-term stability data to establish expiration dating
- Failure to identify or include CQAs or methods for controlling them
- Insufficient data to support use-related risk analysis and any human factors studies associated with the proposed product
- Insufficient data to support drug/device compatibility
- Lack of safety assessment of extractables and leachables, inadequate assessment of extractables and leachables, or submission of that assessment in an unsolicited amendment

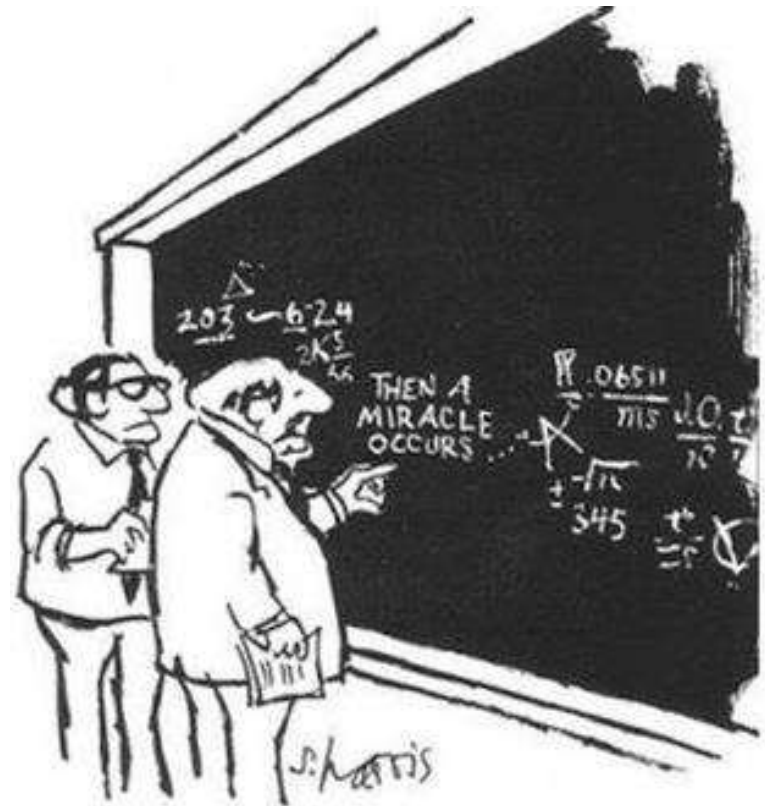


Notable FDA Documents

Topic	Resource Title
Related substance impurities	FDA MAPP 5017.2: Establishing Impurity Acceptance Criteria As Part of Specifications for NDAs, ANDAs, and BLAs Based on Clinical Relevance (January 2018)
Polymorphism	FDA Guidance for Industry: ANDAs: Pharmaceutical Solid Polymorphism (July 2007)
Product design	FDA Guidance for Industry: Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules (June 2015)
Product design	FDA Guidance for Industry: Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (March 2013)
Raw materials/ Excipients	Pharmaceutical Components at Risk for Melamine Contamination (August 2009)
Major deficiencies	FDA Guidance for Industry: ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA (October 2017)

Generic Drug Product Quality Assessment

- We share a common goal
- Ensure that your product can deliver the therapeutic benefit



"I THINK YOU SHOULD BE MORE
EXPLICIT HERE IN STEP TWO."

Acknowledgements

Bhagwant Rege, PhD

*Division Director, Division of Modified Release
Products/OLDP*

Susan Rosencrance, PhD

Director, OLDP

Thank you

