Bioanalytical Methods and Validation: History, Process and Regulatory Perspectives

Patrick J. Faustino, Ph.D.
Lab Chief, Division of Product Quality Research
Office of Testing and Research
Office of Pharmaceutical Quality

June 30, 2020

Disclaimer

- This presentation reflects the views of the author. It should not be construed to represent FDA's views or policies.

Workshop Session

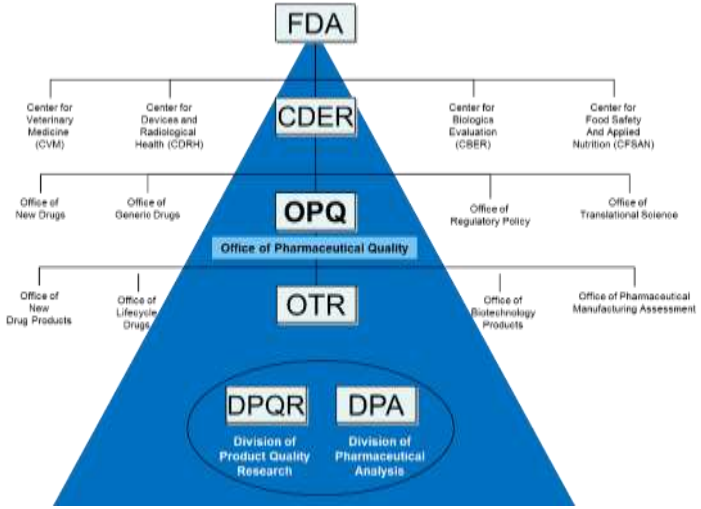
- **Regulated Bioanalysis Workshop: Current Requirements and Expectations**
  - **Office of Pharmaceutical Quality (OPQ) "*Guidance and laboratory perspectives*"**

  - **Presentation 1 (9:15-9:35AM)**
    - *Bioanalytical Method Validation: History, Process, and Regulatory Perspectives (BMV) Guidance*-Dr. Patrick Faustino

  - **Presentation 2 (9:35-9:55AM)**
    - *Regulated Bioanalysis for Large Molecules*-Dr. Jinhui Zhang

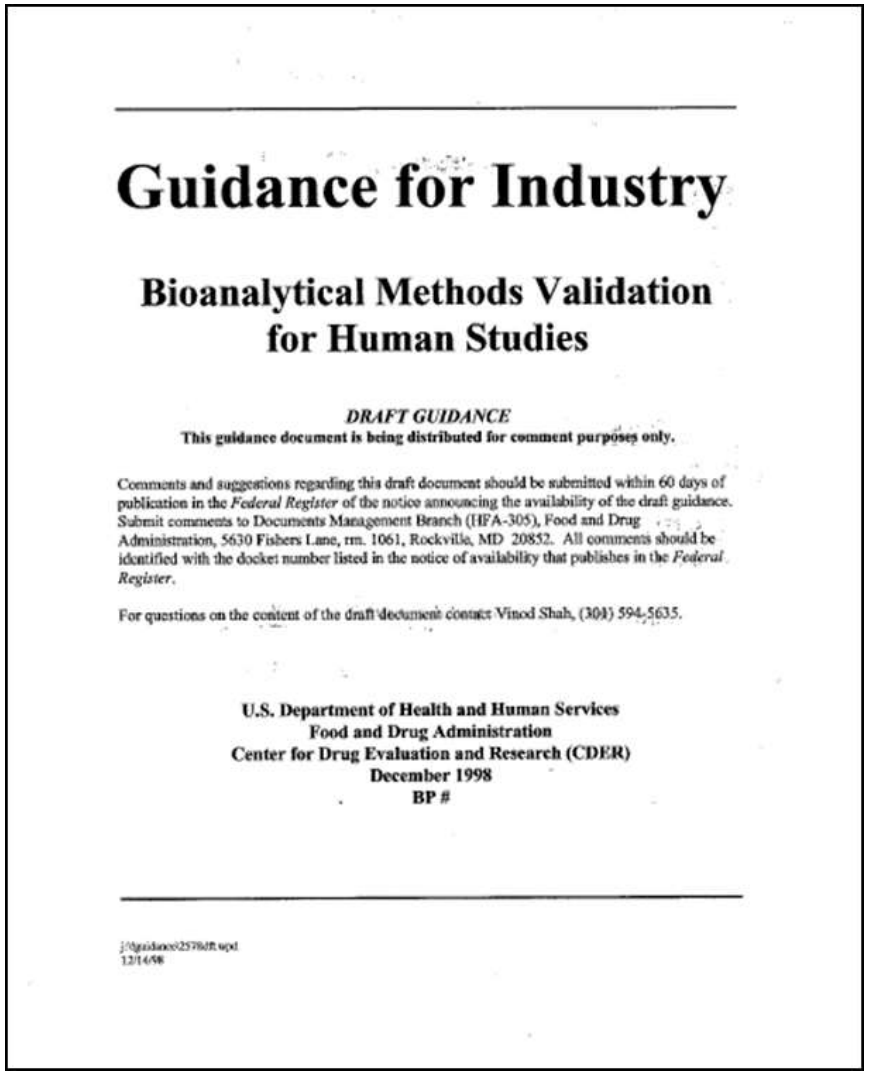
  - **Presentation 3 (9:55-10:15AM)**
    - *Regulated Bioanalysis for Small Molecules*-Dr. Diaa Shakleya

  - **Q & A Discussion (10:15-10:30AM)**
    - *Science based perspectives for the application of the BMV*



Session Objectives

- Participants will be learn about the evolving progress of the bioanalytical method validation guidance,
- ✓participants will be able to: understand the regulatory scope and the importance of bioanalysis in drug development and drug evaluation,
- ✓participants will learn about the FDA regulatory science perspective for bioanalysis and bioequivalence,
- ✓participants will learn why FDA conducts bioanalytical studies and evaluates innovative technologies to:
  - (1) support assessment/review, policy, surveillance and public health issues and
  - (2) advance the regulatory science of bioanalytical method validation.



Guidance for Industry

Bioanalytical Methods Validation for Human Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Documents Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Vinod Shah, (301) 594-5635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
BP #

j:\guidance\2578dft.wpd
12/14/98

Presentation Objectives

- Context for bioanalysis
- Explain the BMV guidance, history, process and procedures
- Provide a foundational understanding of the importance of BMV
- Provide information that can support *Sponsors* and *Researchers*

Bioanalytical Method Validation

U.S. FOOD & DRUG ADMINISTRATION

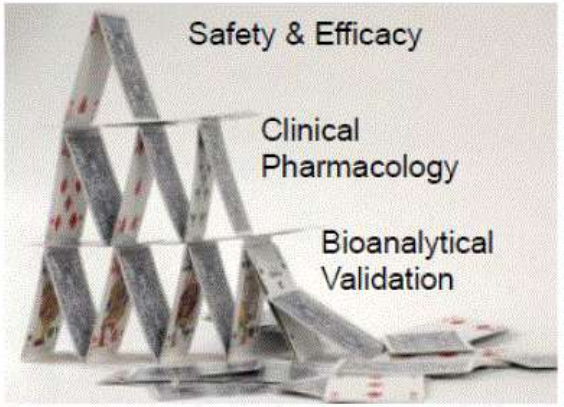
Dr. DeSilvia*

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

House of Cards in Drug Development

To have confidence in the clinical implication of the data, need to have confidence in:

- PK parameters
- Concentration values
- Bioanalytical methods



17

Yu and Bashaw, ***Bioanalysis*** (2014)

- AAPS PharmSci360 (Nov 5, 2018) *The Expanding Frontier of Bioanalysis: New Modalities*

Presentation

- **History of the Guidance**
  - What is a guidance, method validation, regulatory method validation?
  - The guidance history and development
  - Scope and evolution

- FDA Bioanalytical Studies-A regulatory science perspective
  - Who does bioanalytical studies and how
  - How do these studies support FDA regulatory science and policy

- Bioanalytics
  - Evolution and importance
  - Innovation and discussion on existing and emerging bioanalytical technologies

U.S. FOOD & DRUG ADMINISTRATION

First Principles

Presentation

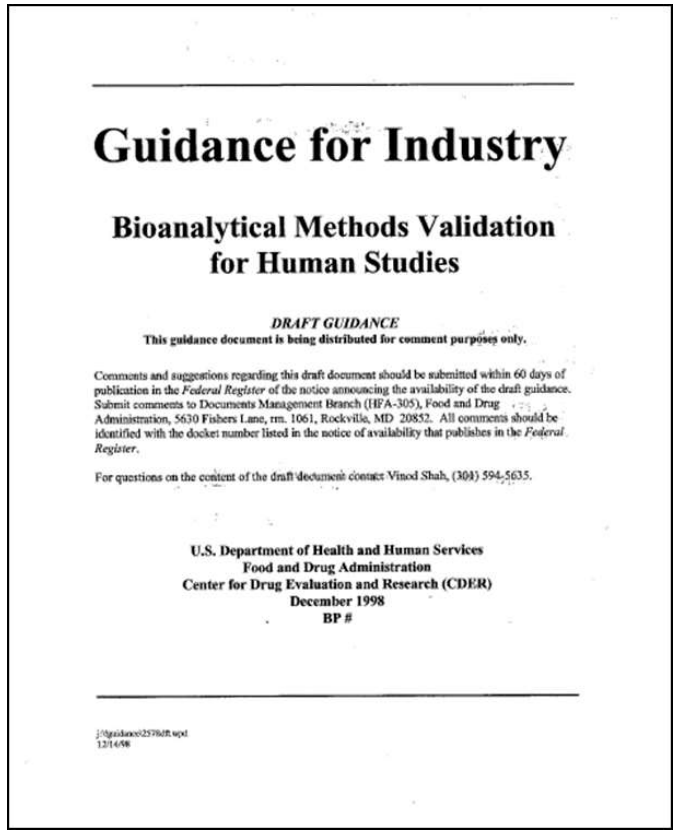
- **Regulatory Guidances**

On March 7, 1996 Federal Register Notice Regulatory Guidances definitions were published for FDA guidances:

The term guidance means:

- **Documents prepared for FDA staff and applicants related to the process, content and evaluation of applications and relating to the design, and testing of regulated products**
- **Documents prepared for FDA personnel and the public that establish policies intended to achieve consistency in the agency's regulatory policy**
- **Documents that establish inspection and enforcement policies and procedures**

- **FDA guidances do not establish legally enforceable responsibilities**
- **Guidances describe the agency's current thinking on a topic and be viewed only as recommendations, unless specific regulatory or statuary requirements are cited: ((21 CFR 211.165(e) and 211.194(a)(2)).**



Guidance for Industry

Bioanalytical Methods Validation for Human Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Documents Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

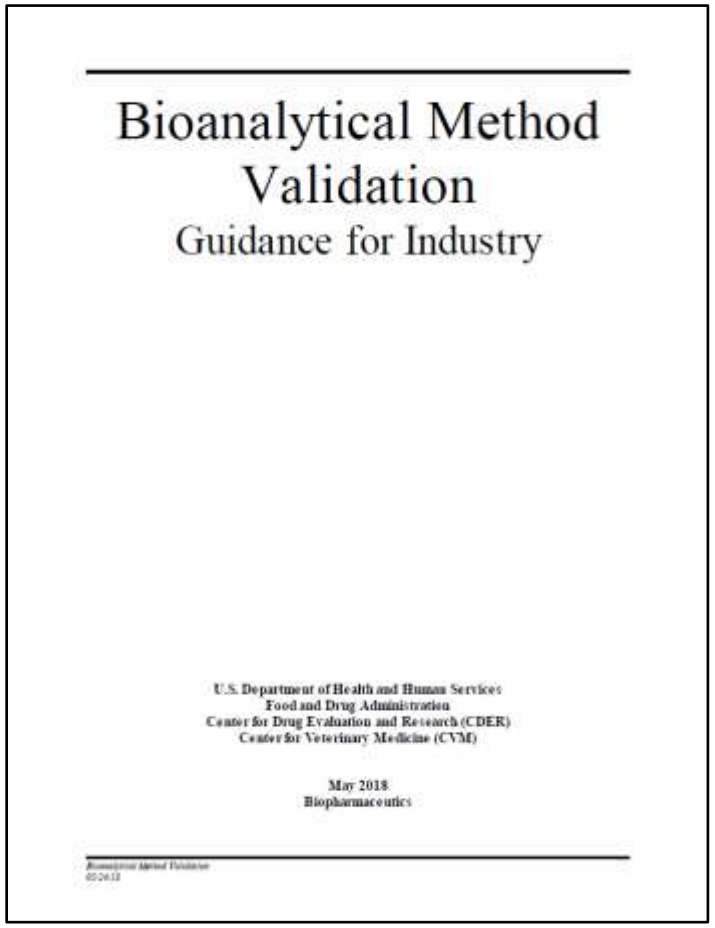
For questions on the content of the draft document contact Vinod Shah, (301) 594-5635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
BP #

Analytical Method Validation

What is Validation?

- **Method validation** is the process of demonstrating that analytical procedures are suitable for their intended purpose
- **Regulatory Method Validation** is the process of demonstrating that analytical procedures submitted in an NDA or ANDA are suitable for their intended use
- **Analytical Method Validation** includes all the procedures recommended to demonstrate that a particular method for the quantitative measurement of an analyte in a given biological matrix, such as blood, plasma, urine, is reliable and reproducible-*Bioanalytical Method Validation Guidance Dec 1998*.
- **Bioanalytical Method Validation-**Bioanalytical method validation proves that the optimized method is suited to the analysis of the study samples. *Bioanalytical Method Validation Guidance May 2018*.


Bioanalytical Method Validation

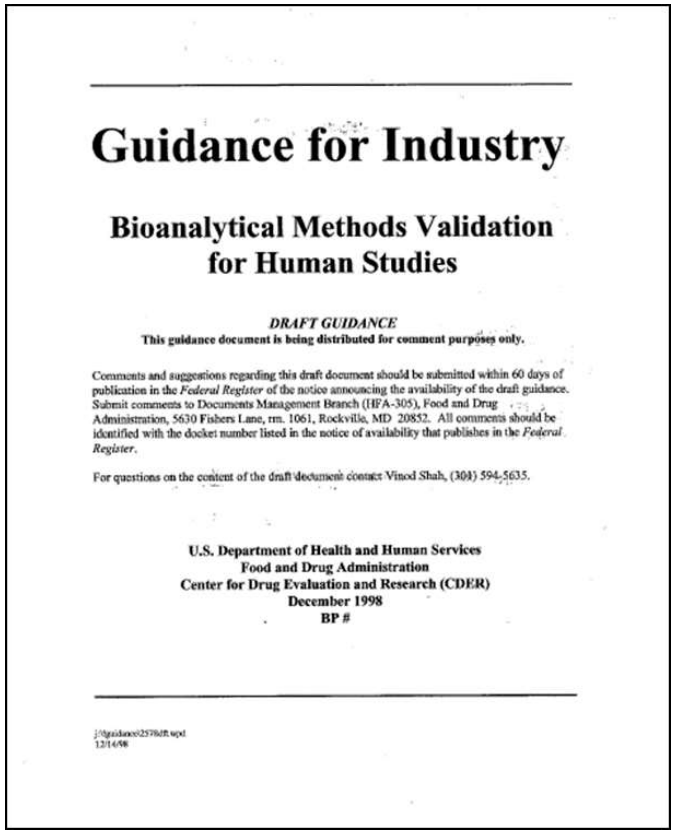
Guidance for Industry

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

May 2018
Biopharmaceutics

Presentation

- **History of the Guidance**



Guidance for Industry

Bioanalytical Methods Validation for Human Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Documents Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

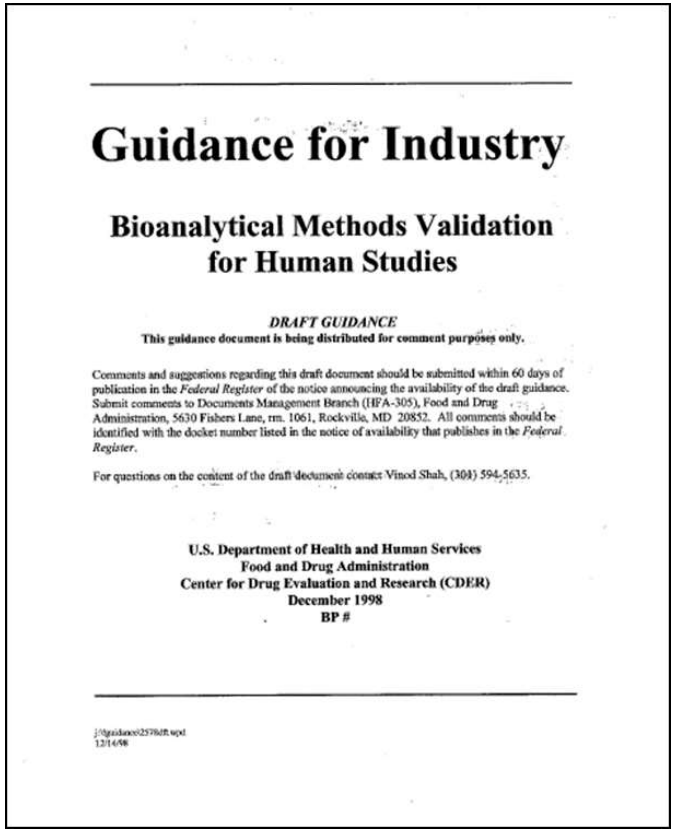
For questions on the content of the draft document contact Vinod Shah, (301) 594-5635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
BP #

- The 1998 draft of the BMV was based primarily on the Workshop-***Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic studies***, held on December 3-5, 1990 at Crystal City, VA.
- The meeting was sponsored by AAPS, US FDA and Federation Internationale Pharmacetique, Canadian Health Protection Branch and the Association of Official Analytical Chemists (AOAC).
- The guidance was prepared by the CDER Biopharmaceutics Coordinating Committee and the Clinical Pharmacology Section of the Medical Policy Coordinating committee in CDER and staff from CDER's Laboratory of Clinical Pharmacology.

Presentation

- **History of the Guidance**



Guidance for Industry

Bioanalytical Methods Validation for Human Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Documents Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

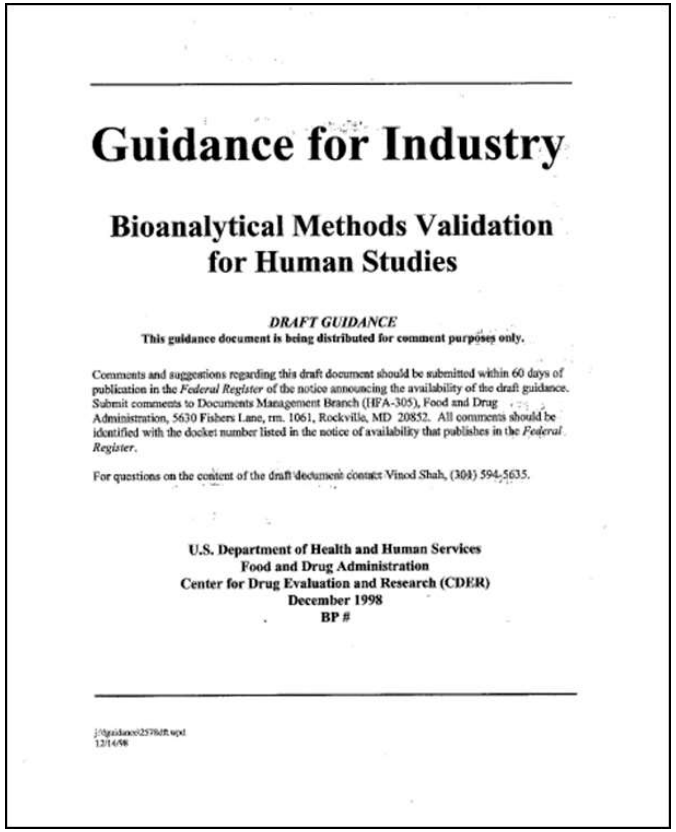
For questions on the content of the draft document contact Vinod Shah, (304) 594-5635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
BP #

- The 1998 draft of the BMV was based primarily on the AAPS Workshop-***Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic studies***, held on December 3-5, 1990 at Crystal City, VA.
- The AAPS Workshop- ***Bioanalytical Methods Validation A Revisit With a Decade of Progress***, Crystal City, VA on January 3-5, 2000 was held shortly after the guidance draft.
- Many of the issues discussed were: acceptance criteria, partial or full validation, stability, bridging studies, calibration models, authentication of standards, outliers, spiked vs incurred samples, new technologies LC to LC-MS (i.e. ion suppression) and this thing called matrix effect.

Presentation

- **History of the Guidance**



Guidance for Industry

Bioanalytical Methods Validation for Human Studies

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Documents Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions on the content of the draft document contact Vinod Shah, (301) 594-5635.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
December 1998
BP #

j:\guidance\2578dft.wpd
12/14/98

*Ayers, G., D. Burnett, A. Griffiths, and A. Richens, "**Quality Control of Drug Assay**," Clin Pharmacokinetics 1981; 6:106-117.*

***Brooks, M.A. and R.E. Weifeld, "**A Validation Process for Data from the Analysis of Drugs in Biological Fluids," Drug Development and Industrial Pharmacy 1985; 11: 1703-1728.*

*Buick, A.R., M.V. Doig, S.C. Jeal, G.S. Land, and R.D. McDowall, **"Method Validation in the Bioanalytical Laboratory**," Journal of Pharmaceutical and Biomedical Analysis 1990; 8:629-637.*

*Karnes, S.T., G. Shiu, and V.P. Shah, "**Validation of Bioanalytical Methods**," Pharmaceutical Research 1991; 8:421-426.*

*Mehta, A. C., "**The Validation Criteria for Analytical Methods used in Pharmacy Practice Research**," J Clin Pharm Ther 1989; 14:465-473.*

*Pachla, L.A., D.S. Wright, and D.L. Reynolds, "**Bioanalytical Considerations for Pharmacokinetic and Biopharmaceutic Studies**," J Clin Pharmacol 1986; 26:332-335.*

*Shah, V.P., K.K. Midha, S.V. Dighe, et al**., Analytical Methods Validation: Bioavailability, Bioequiva1ence and Pharmacokinetic Studies** (Conference report). Pharmaceutical Research 1992; 9:588-592.*

*Taylor, J.K., "**Validation of Analytical Methods**," Analytical Chemistry 1983; 55:600A-608A.*

*Timm, U., M. Wall, and D. Dell, "**A New Approach for Dealing with the Stability of Drugs in Biological Fluids**," J Pharm Sci 1985; 74:972-977.*

The United States Pharmacopeia XXII: Validation of Compendial Methods, USP Convention Inc. 1990; 1710.

History of the Guidance

- AAPS Conference-***Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic studies***, Crystal City, VA on December 3-5, 1990.
- Federal Register Notice-Regulatory Guidances definitions were published for FDA Guidances on March 7, 1996.
- FDA Draft Guidance- ***Bioanalytical Methods Validation for Human Studies***, December 1998.
- AAPS Workshop- ***Bioanalytical Methods Validation A Revisit With a Decade of Progress***, Crystal City, VA on January 3-5, 2000.
- AAPS Workshop- ***Bioanalytical Methods Validation For Macromolecules***, held at Crystal City, VA on March 1-3, 2000.
- FDA Draft Guidance- ***Bioanalytical Method Validation***, May 2001.
- AAPS Workshop- ***Quantitative Bioanalytical Methods Validation and Implementation: Best practices for Chromatographic and Ligand Binding Assays***, held at Crystal City, VA on May 1-3, 2006.

History of the Guidance

- AAPS *Workshop*- ***AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples—Implications of Crystal City Recommendations*** held at Crystal City, VA on May 1-3, 2008.
- AAPS *Workshop*- ***Quantitative Bioanalytical Method Validation and Implementation: The 2013 Revised FDA Guidance*** held at Crystal City, VA on December, 2013
- FDA Draft Guidance- Bioanalytical Methods Validation for Human Studies, September 2013
- FDA Guidance- ***Bioanalytical Methods Validation Guidance for Industry***, May 2018
- AAPS-ICH Conference-Harmonized Draft Guidance ICH-M10- ***Bioanalytical Method Validation*** June 10-12, 2019
- FDA Draft Guidance for Industry- ***Evaluation of Internal Standard Responses During Chromatographic Bioanalysis: Questions and Answers***, September 2019

History of the Guidance

Conference Reports CC-I-V

- AAPS Conference-***Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic studies***, December 3-5, 1990. **Crystal City-I**
- Federal Register Notice-Regulatory Guidances definitions were published for FDA Guidances on March 7, 1996.
- FDA Draft Guidance- ***Bioanalytical Methods Validation for Human Studies***, December 1998.
- AAPS Workshop- ***Bioanalytical Methods Validation A Revisit With a Decade of Progress***, Crystal City, VA on January 3-5, 2000. **Crystal City-II**
- AAPS Workshop- ***Bioanalytical Methods Validation For Macromolecules***, held at Crystal City, VA on March 1-3, 2000.
- FDA Draft Guidance- Bioanalytical Methods Validation for Human Studies, May 2001.
- AAPS Workshop- ***Quantitative Bioanalytical Methods Validation and Implementation: Best practices for Chromatographic and Ligand Binding Assays***, May 2006. **Crystal City-III**
- AAPS *Workshop*- ***AAPS Workshop on Current Topics in GLP Bioanalysis: Assay Reproducibility for Incurred Samples—Implications of Crystal City Recommendations*** May 1-3, 2008. **Crystal City-IV**
- AAPS *Workshop*- ***Quantitative Bioanalytical Method Validation and Implementation: The 2013 Revised FDA Guidance*** held at Crystal City, VA on December, 2013 **Crystal City-V**
- FDA Draft Guidance- Bioanalytical Methods Validation for Human Studies, September 2013
- FDA Guidance- ***Bioanalytical Methods Validation Guidance for Industry***, May 2018
- AAPS Workshop-ICH Harmonized Draft Guidance M10- ***Bioanalytical Method Validation*** Silver Spring, MD**.** June 10-12, 2019

- FDA Draft Guidance for Industry- ***Evaluation of Internal Standard Responses During Chromatographic Bioanalysis: Questions and Answers***, September 2019

History of the Guidance

Conference Reports

Pharmaceutical Research, Vol. 17, No. 12, 2000 *Research Article*

Workshop/Conference Report

Bioanalytical Method Validation—A Revisit with a Decade of Progress

Vinod P. Shah,[1] Kamal K. Midha,[2,10] John W. A. Findlay,[3] Howard M. Hill,[4] James D. Hulse,[5] Iain J. McGilveray,[6] Gordon McKay,[2] Krys J. Miller,[7] Rabindra N. Patnaik,[1] Mark L. Powell,[8] Alfred Tonelli,[9] C. T. Viswanathan,[1] and Avraham Yacobi[10]

Received July 31, 2000; accepted September 14, 2000

PURPOSE OF THE REPORT

This report is a synthesis of (1) the earlier conference on Analytical Methods Validation–Bioavailability, Bioequivalence and Pharmacokinetic Studies (Conference held in Arlington, VA, December 3–5, 1990 and the report published in Pharmaceutical Research, 9: 588-592, 1992) and (2) the workshop on "Bioanalytical Methods Validation—A Revisit with a Decade of Progress," (Workshop held in Arlington, VA, January 12–14, 2000), sponsored by the American Association of Pharmaceutical Scientists and the U. S. Food and Drug Administration. The bioanalytical method validation workshop of January 12–14, 2000 was directed towards small molecules. A separate workshop was held in March 1–3, 2000 to discuss validation principles for macromolecules. The purpose of this report is to represent the progress in analytical methodologies over the last decade and assessment of the major agreements and issues discussed with regard to small molecules at both the conference and the workshop. The report is also intended to provide guiding principles for validation of bioanalytical methods employed in support of bioavailability, bioequivalence, and pharmacokinetic studies in man and in animals.

OBJECTIVES

The objectives of the conference and the workshop were as follows:

- To agree on what should be required in bioanalytical method validation and the procedures to establish validation.
- To determine processes of application of the validation procedures in bioavailability, bioequivalence and pharmacokinetics studies.
- To review the progress, impact and advances made during the last decade of bioanalytical methods vali-

The AAPS Journal (2020) 22: 10
DOI: 10.1208/s12248-019-0398-7

Meeting Report

AAPS Workshop Report on ICH M10

Brian Booth,[1] Faye Vazvaei,[2,5] Eric Fluhler,[3] Heather Myler,[4] and Eric Woolf[2]

Received 28 October 2019; accepted 4 November 2019; published online 10 December 2019

Abstract Over the last decade, several regulatory guidelines on bioanalytical method validation (BMV) have been issued by regulatory agencies around the world. This has left the bioanalytical community struggling with regional differences in regulatory expectations when preparing for global pharmaceutical submissions. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) has the mission to achieve greater harmonization worldwide to ensure that safe, effective, and high-quality medicines are developed and registered in the most resource-efficient manner. Following calls for harmonization, ICH-selected bioanalytical method validation and sample analysis among its topics for guidance development and earlier this year released a draft guideline (M10) on BMV for public consultation. In response, the American Association of Pharmaceutical Scientists (AAPS) held a 3-day workshop to provide a forum for regulatory, industry, and academic scientists to discuss the guideline and hear various points of view on key aspects. While there was agreement that the draft guideline is generally well written and comprehensive, specific topics generated considerable discussion and, in some cases, revision recommendations for consideration by the expert working group (EWG) responsible for the guideline content. This report provides a summary of the workshop proceedings.

INTRODUCTION

In February 2019, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) released a draft harmonized guideline (M10) on bioanalytical method validation (BMV) for public consultation. In its continuing efforts to support excellence in the pharmaceutical sciences, the American Association of Pharmaceutical Scientists (AAPS), in collaboration with the European Bioanalysis Forum (EBF), Japan Bioanalysis Forum (JBF), and China Bioanalysis Forum (CBF), organized a workshop for stakeholders from industry, academia, and health authorities to discuss and provide collective feedback on the draft guideline. This was the second in a series of sister workshops organized by the previously mentioned regional bioanalytical groups. The first forum in this series, organized by EBF, was held in May 2019 in Barcelona, Spain.

This article provides a summary of the workshop and the sections of the draft guideline that stimulated the most discussion. The discussions and proposed changes described in this manuscript summarize the views of the AAPS members in attendance and do not necessarily reflect the views or policies of the FDA or ICH M10 EWG or the authors. Furthermore, the proposed changes do not necessarily indicate that consensus was reached by all workshop participants but do provide substrate for consideration by the ICH EWG responsible for the guidance.

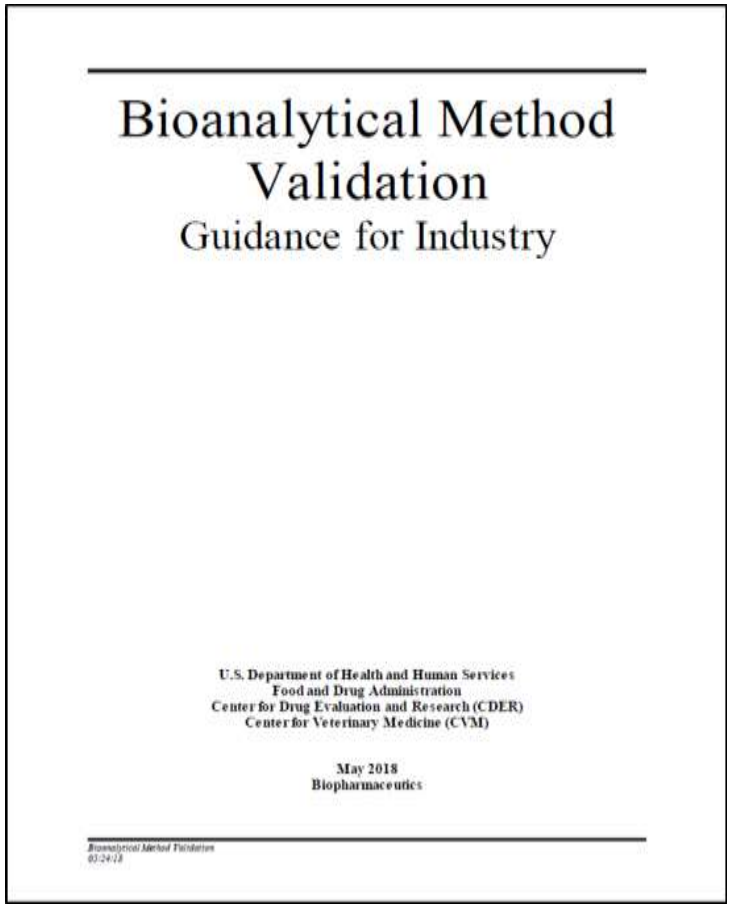
BACKGROUND

It has long been recognized that bioanalysis plays an important, even critical, role in drug development and the regulatory approval process. Aiming to ensure that the best scientific practices are embraced, the bioanalytical community (industry, academic, and health authority scientists) has been actively engaged in discussions of best practices over the years. In the USA, this dialogue has, to a large extent, taken the form of multiday workshops. AAPS and the FDA have co-sponsored several of these workshops (commonly referred to as the Crystal City Meetings), the outputs of which were published (1–5) and served as substrate for consideration in development and revision of FDA regulatory guidance. (6,7) While the 2001 FDA guidance on BMV served as an industry benchmark for chromatographic assays for several years, numerous health authorities have since published their own

[1] Office of Translational Sciences, Office of Clinical Pharmacology, CDER, US FDA, Silver Spring, Maryland, USA.
[2] Department of Pharmacokinetics, Pharmacodynamics and Drug Metabolism, Merck & Co., Inc., West Point, Pennsylvania, USA.
[3] BA-PK Compliance Associates, LLC, Washingtonville, New York, USA.
[4] Immunochemistry Department, PPD Laboratories, Richmond, Virginia, USA.
[5] To whom correspondence should be addressed. (e-mail: Fataneh.Vazvaei-Smith@Merck.com)

Presentation

- **Scope of the Guidance**


Bioanalytical Method Validation
Guidance for Industry

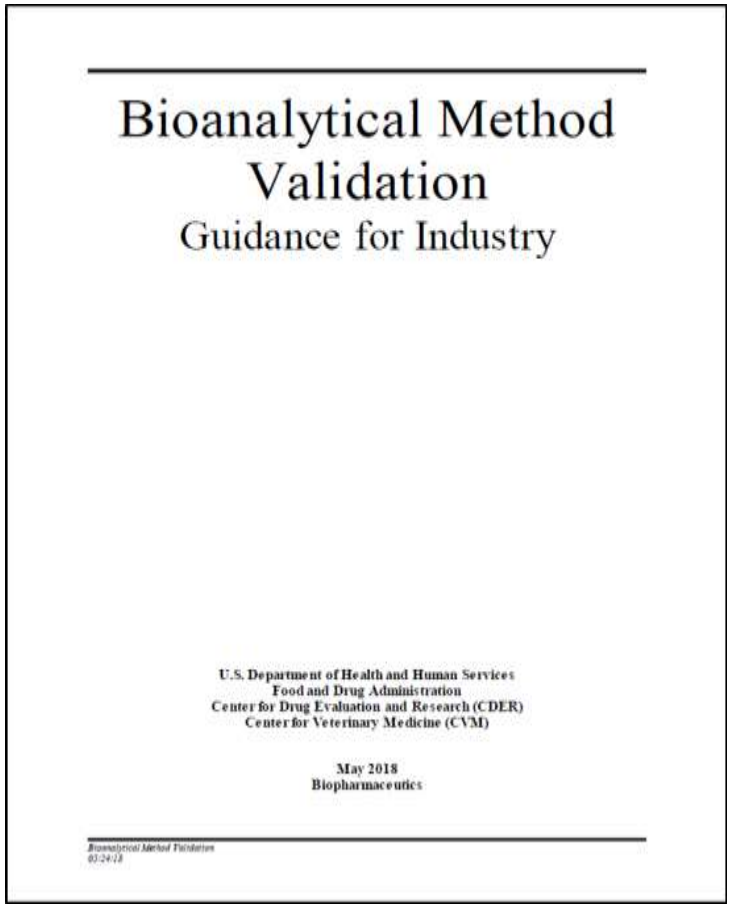
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics

- Clinical Studies-BA, BE, and PK, toxicokinetic, biomarkers
- Applications- INDs, BLAs, NDAs, ANDAs,
- Non-clinical studies-BA, BE and PK in blood and urine
- INADs, NADAs and ANADAs
- Applies to chromatographic procedures (CCs) and ligand binding assay (LBAs)-that determine the level of drugs, metabolites, biomarkers …

Presentation

- **Process and Procedures**


Bioanalytical Method Validation
Guidance for Industry

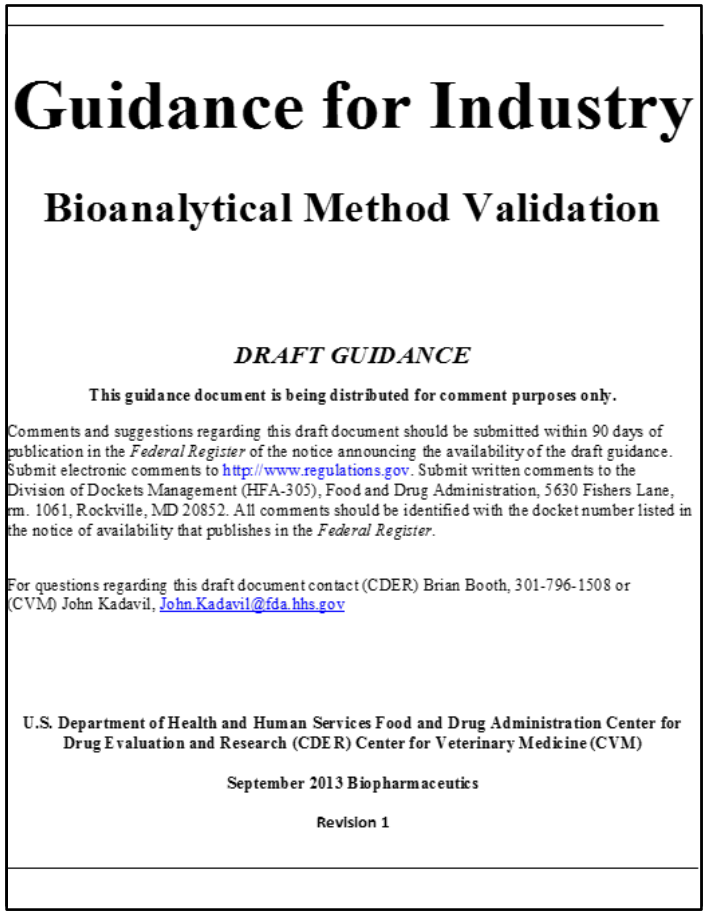
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

May 2018
Biopharmaceutics

- Method Development
- Method Validation
  - Accuracy
  - Precision
  - Linearity
  - Analytical Range
  - Specificity
- Stability
- Procedures, HPLC, HPLC-MS, HPLC-MS/MS, GC-MS, Advanced bioanalytics
- Fit-for-purpose

Presentation

- **Evolution of the Guidance**



Guidance for Industry

Bioanalytical Method Validation

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

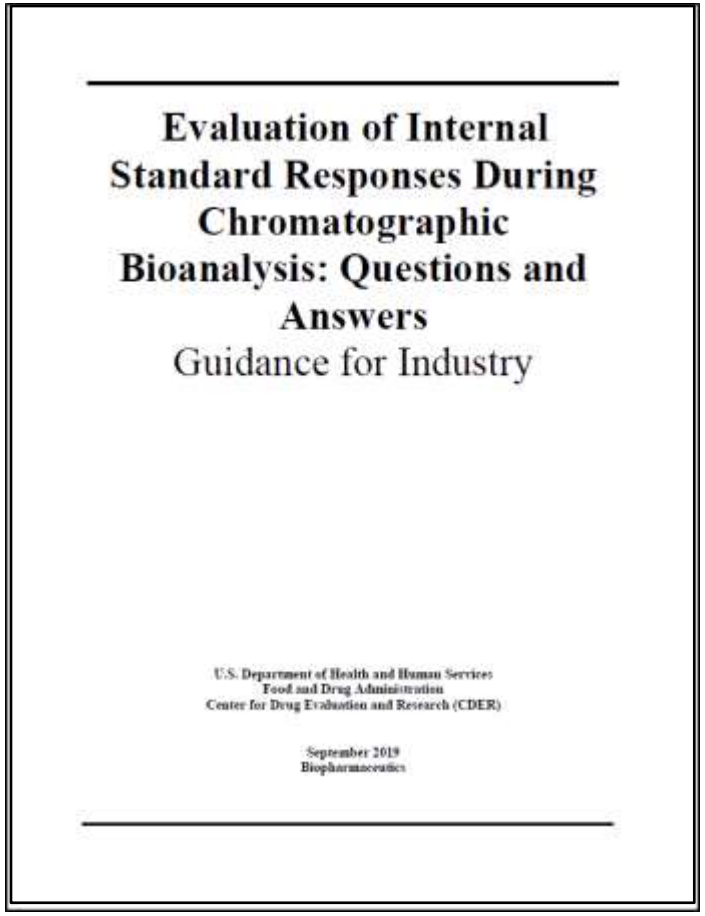
Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Brian Booth, 301-796-1508 or (CVM) John Kadavil, John.Kadavil@fda.hhs.gov

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

September 2013 Biopharmaceutics

Revision 1

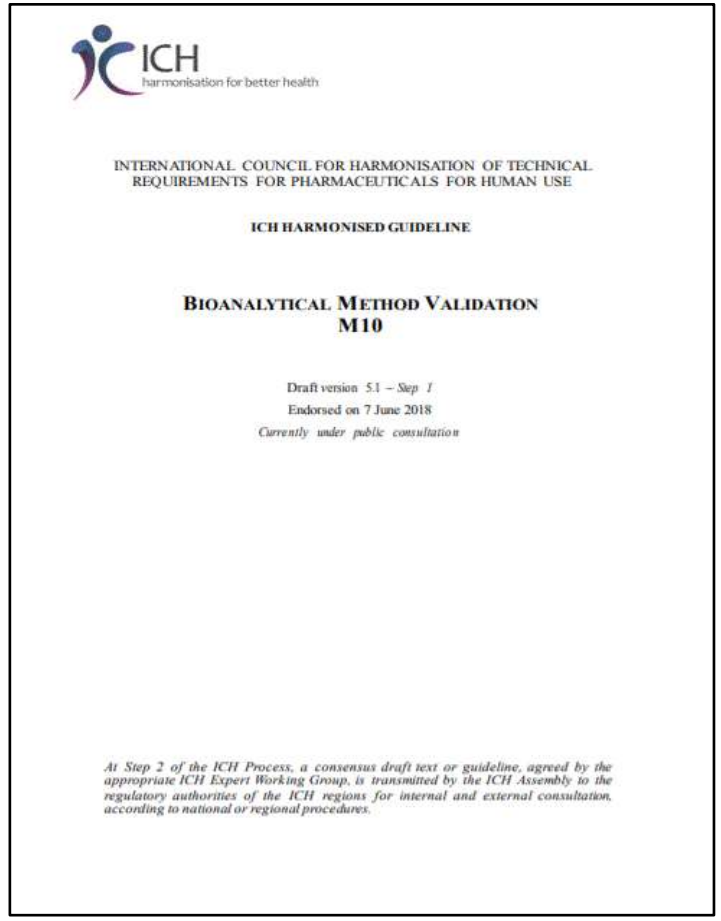


Evaluation of Internal Standard Responses During Chromatographic Bioanalysis: Questions and Answers

Guidance for Industry

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

September 2019
Biopharmaceutics



ICH harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

BIOANALYTICAL METHOD VALIDATION
M10

Draft version 5.1 – *Step 1*
Endorsed on 7 June 2018
Currently under public consultation

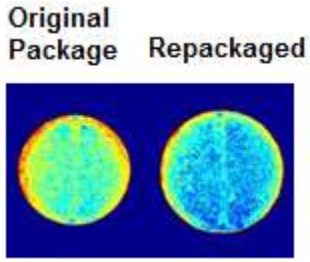
At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

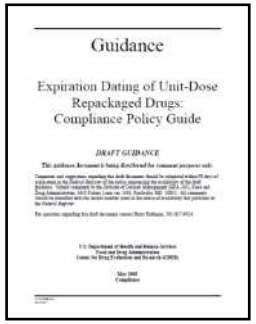
Presentation

- History of the Guidance
  - Development
  - Scope
  - Evolution
- **FDA Bioanalytical Studies-A regulatory science perspective**
  - Who does bioanalytical studies and how
  - How do these studies support FDA regulatory science and policy
- Bioanalytics
  - Evolution and importance
  - Innovation and discussion on emerging bioanalytical technologies

FDA Bioanalytical Studies

- **A Regulatory Science Perspective**
  - ***Regulatory science** is a scientific discipline consisting of the development and application of scientific methods, tools, approaches, and other relevant processes derived from various scientific disciplines used to support regulatory and other policy objectives*
  - ***Regulatory research** is focused on protecting and promoting the public health, **identifying emerging technology, speeding innovation, while principally supporting** review, policy and compliance, surveillance **needs and requirements***




Guidance

Expiration Dating of Unit-Dose Repackaged Drugs: Compliance Policy Guide

DRAFT GUIDANCE

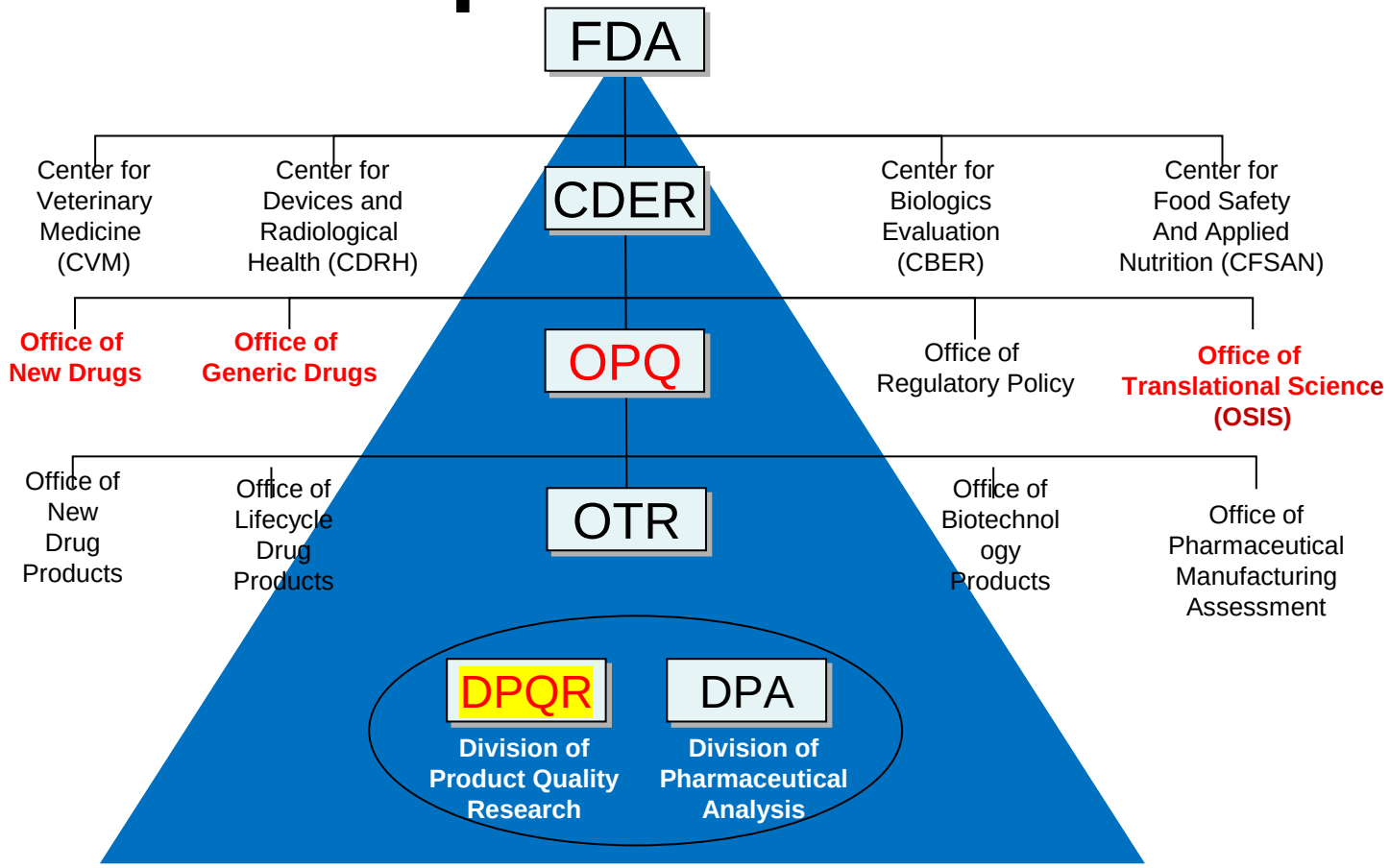

THE WALL STREET JOURNAL.

FDA Withdraws Approval of a Generic Version of Wellbutrin

Bioequivalence evaluation of innovator and generic Bupropion XL marketed drug products

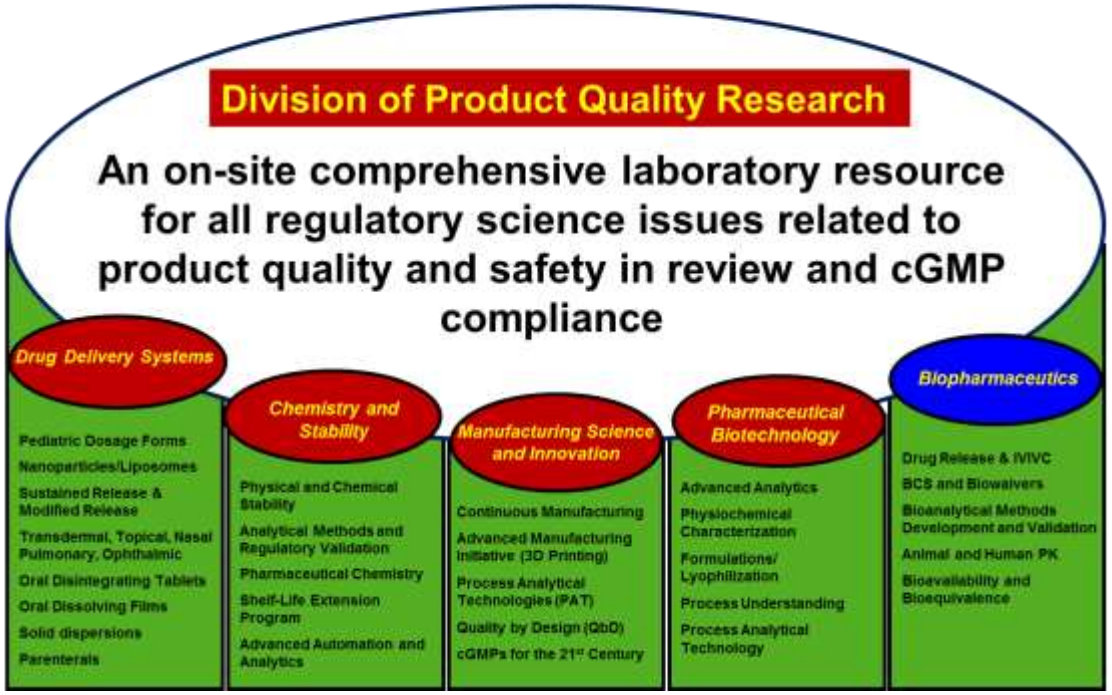
FDA Bioanalytical Studies

- **A Regulatory Science Perspective**
  - Who does bioanalytical studies?



FDA Bioanalytical Studies

- **A Regulatory Science Perspective**
  - How does OTR-DPQR conduct bioanalytical studies?

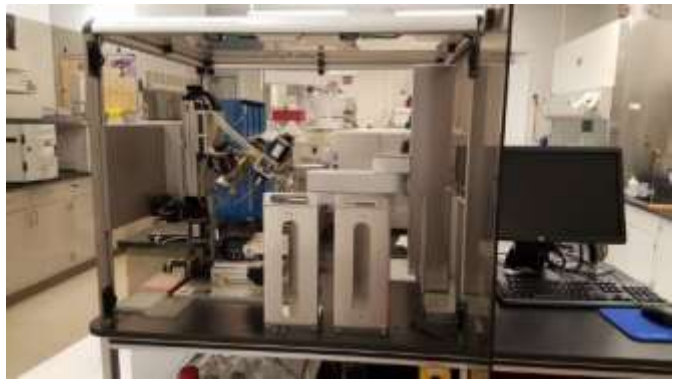


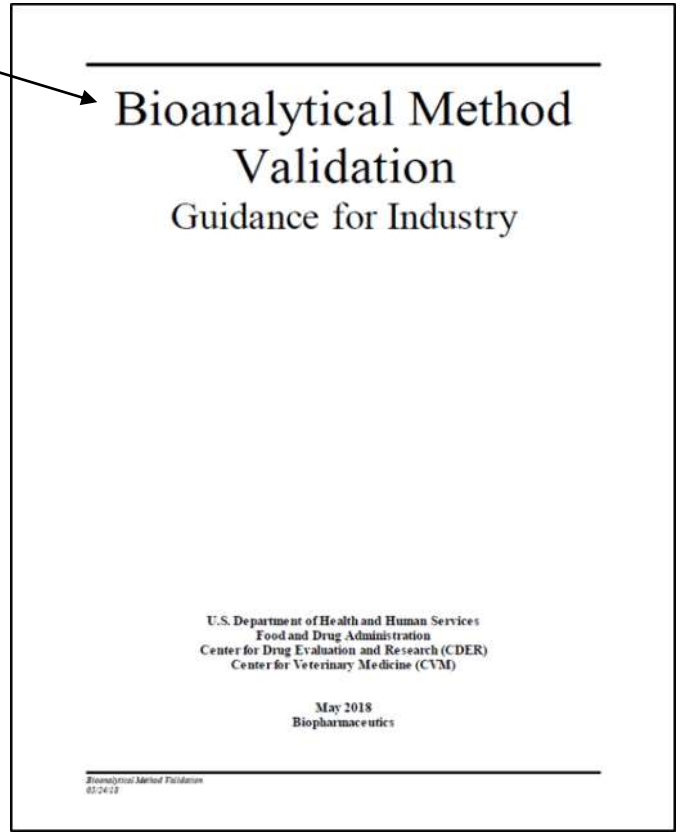
Bioanalytical Program

- *Bioanalytical (MV) Team*
- *Mass Spectroscopy Team*
- *Chromatography Team*
- *Rapid Response Complex Method Development Team*
- *Synthesis Team*
- *Advanced Analytics Team*

FDA Bioanalytical Studies

- **A Regulatory Science Perspective**
  - Translating CDER research to support assessment, policy
    - ***and Sponsors!***





Bioanalytical Method Validation

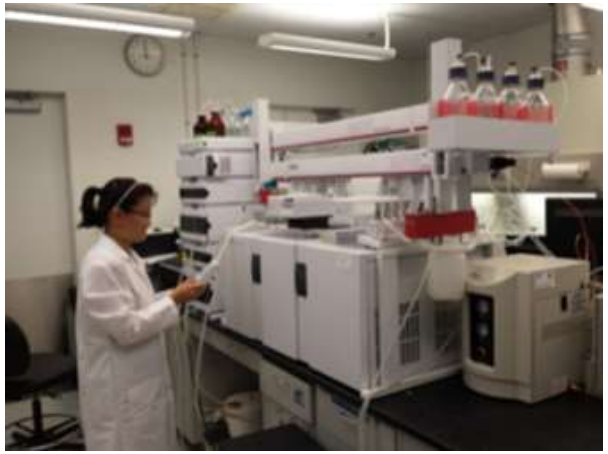
Guidance for Industry

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

May 2018
Biopharmaceutics

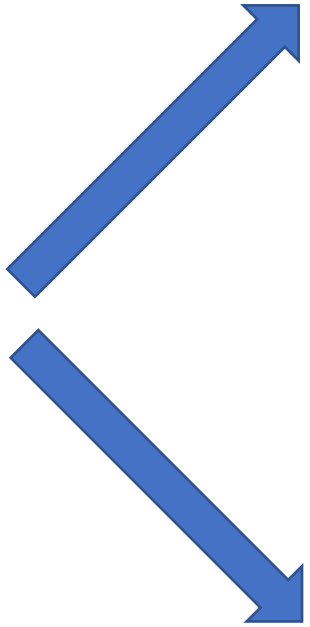
FDA Bioanalytical Studies

- **A Regulatory Science Perspective**
  - Guidance Support
  - Medical Counter Measures
  - Product Performance
  - Public Health
  - Surveillance



Presentation

- **Regulatory Guidance Support**



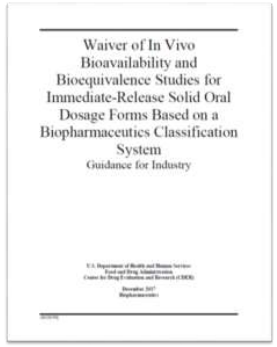
P.J. Faustino, AB. Ciavarella, RC. Lyon and A.S. Hussain ***Bioanalytical Methods Validation: A Laboratory Case Study Illustrating the Application of the FDA/CDER "Guidance for Industry"*****. FDA Science Forum. AH-03. Washington, D.C., April 2002.**

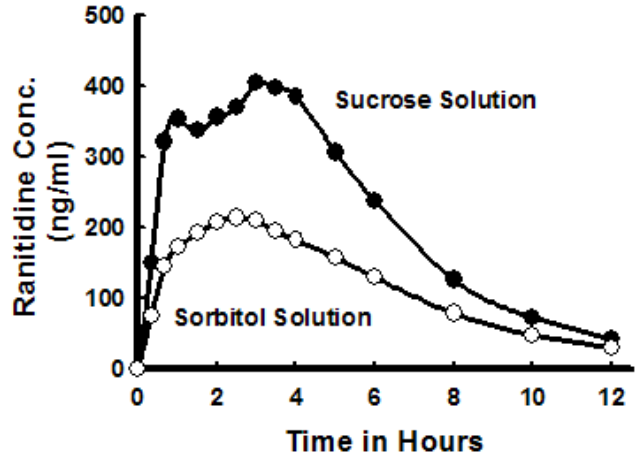
FDA Bioanalytical Studies

- **Regulatory Guidance Support**

Clinical Studies-Excipient Effect

- **Clinical Endpoint**: Bioavailability
- **Regulatory Objective**: Effect of osmotic excipients
- **Research Outcome**: *Bioavailability of BCS Class I high permebility drug not affected by osmotic excipient*- ***BCS class III AUCs reduced >50%***
- **Regulatory Outcome**: Importance of examining excipient effect on drug absorption-advanced the regulatory science of excipients excipient effects-advised assessors to ***evaluate high risk excipients*** during review of in vivo BA or BE studies and biowaivers for BCS Class III compounds


Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System
Guidance for Industry



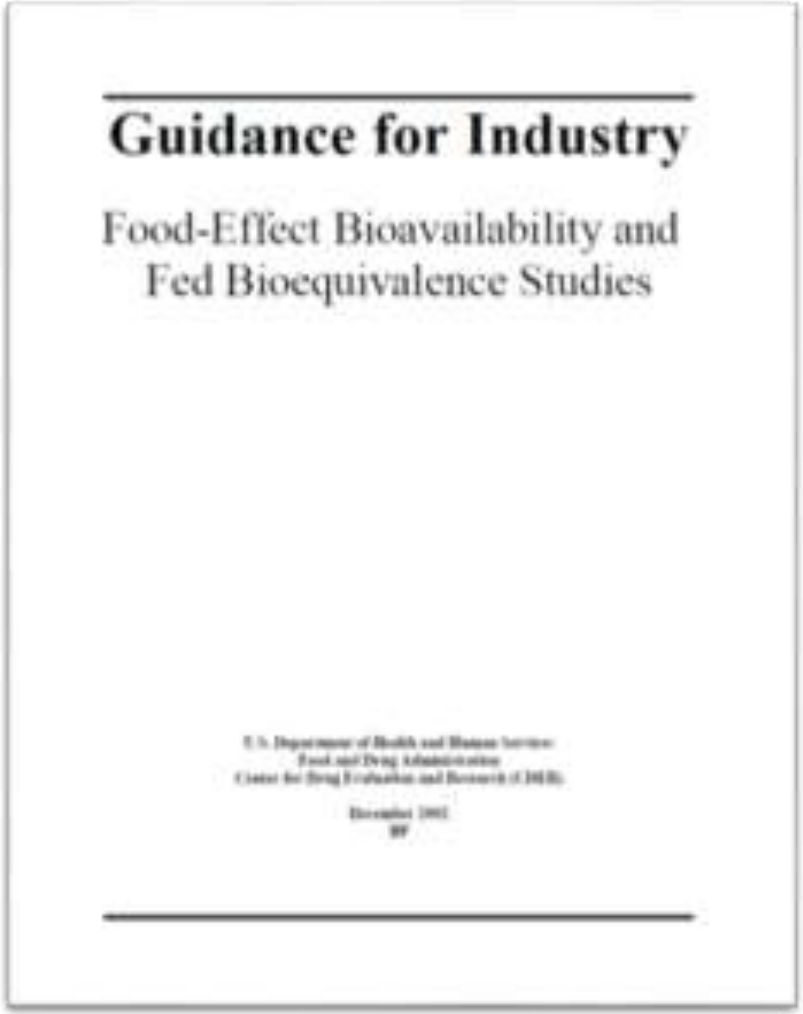
A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol. Pharm. Res. 24(1) January (2007) 73-80

FDA Bioanalytical Studies

- **Regulatory Guidance Support**

Clinical Study-Food Effect Studies

- **Clinical Endpoint**: Bioequivalence
- **Regulatory Objective**: Effect of Food on a Class I Drug
- **Research Outcome***: Bioequivalence of BCS Class I Propranolol Drug Products not affected by Food*
- **Regulatory Outcome**: Information provided to CDER assessors/reviewers of the importance of examining foodeffects on drug absorption for clinical studies: waiver of in vivo BA or BE studies


Guidance for Industry

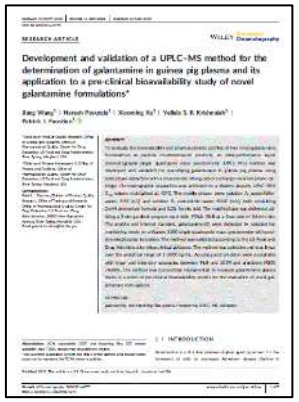
Food-Effect Bioavailability and Fed Bioequivalence Studies

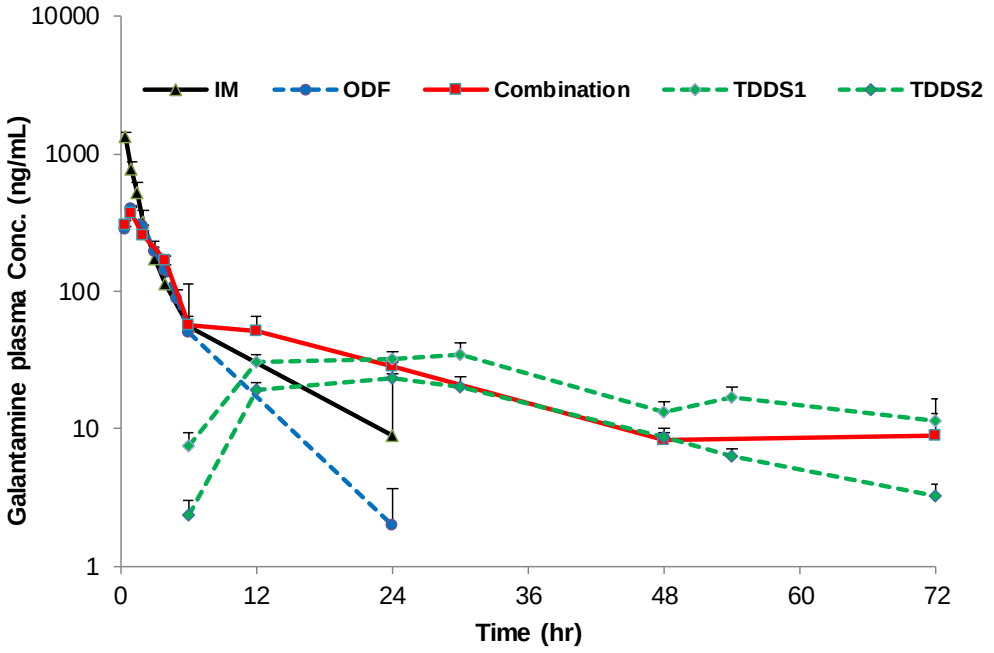
FDA Bioanalytical Studies

- **Medical Counter Measures**

Pre-Clinical Study-Galantamine

- **Study Endpoint**: Bioavailability
- **Regulatory Objective**: Evaluate novel galantamine formulations as a prospective medical counter-measure for use in the event of a nerve agent attack. (DOD-FDA MCM project)
- **Research Outcome**: *Both galantamine oral dissolving film and transdermal drug delivery systems (TDDS) were bioavailable*
- **Regulatory Outcome**: Galantamine oral dissolving films can provide ***a fast drug release*** (in theater) and TDDS formulations can provided ***prolonged drug release*** (In theater and for civilian populations)


Development and validation of a UPLC–MS method for the determination of galantamine in guinea pig plasma and its application to a pre-clinical bioavailability study of novel galantamine formulations*



FDA Bioanalytical Studies

- **Product Performance**

Clinical Study-Bupropion

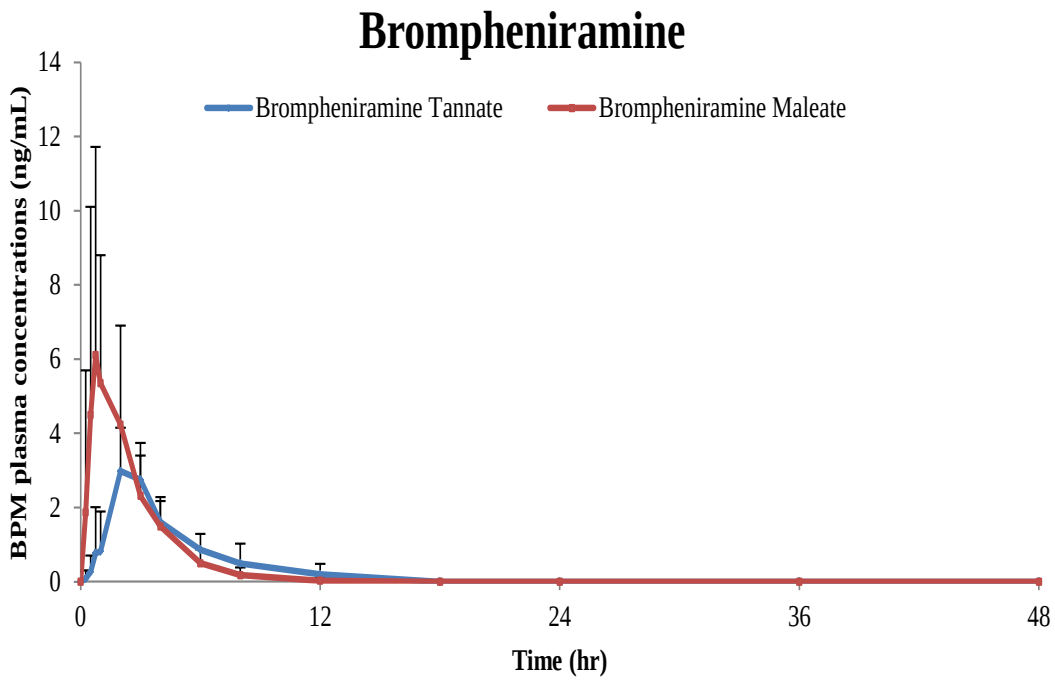
- **Clinical Endpoint**: Bioequivalence
- **Regulatory Objective**: Evaluation of Innovator and Generic Bupropion XL Drug Products
- **Research Outcome**: The study results determined that the generic drug (TEST) product was not bioequivalent to the innovator (RLD)
- **Regulatory Outcome**: ***The rating was changed and the generic product was removed from the market***

FDA Bioanalytical Studies

- **Public Health**

Pre-clinical Study-Brompheniramine

- **Study Endpoint**: Bioequivalence
- **Regulatory Objective**: Evaluation of an in-house manufactured brompheniramine taste masked formulation to enhance compliance for pediatric patients
- **Research Outcome**: ***The PK profiles were not significantly different between the brompheniramine taste masked formulation and the commercial available formulation***
- **Public Health Outcome**: Support the NIH-FDA Pediatric Formulation Initiative for the assessment of critical product quality attributes to advance the safety and efficacy profiles of pediatric products globally

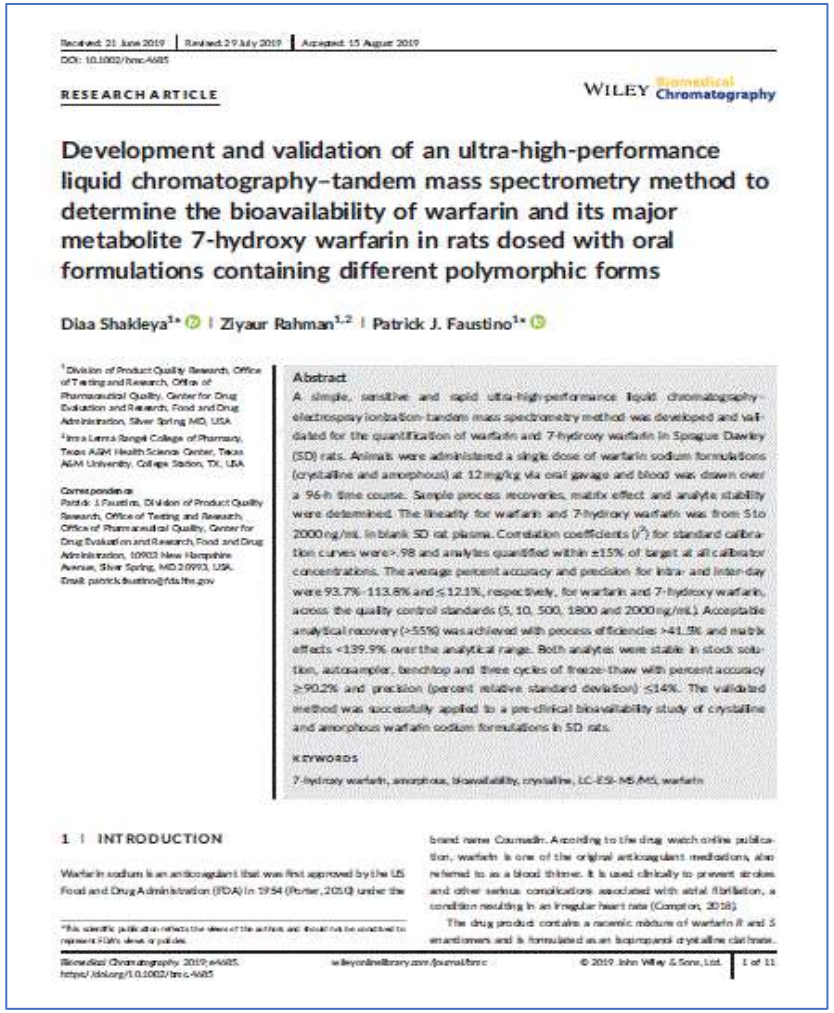


FDA Bioanalytical Studies

- **Public Health**

Pre-Clinical Study-Warfarin

- **Study Endpoint**: Bioavailability
- **Regulatory Objective**: Compare the PK profiles between the clathrate (crystalline form) and the amorphous polymorph form and establish a link between changes in product quality and bioavailability
- **Research Outcome**: *Prolonged elimination half-life of 7-OH warfarin (15 vs 25hr) was observed for the amorphous formulation compared to clathrate formulation.*
- **Regulatory Outcome**: Changes to the product quality (Warfarin API form) may alter the elimination profiles of active and inactive metabolites



Received: 21 June 2019 | Revised: 29 July 2019 | Accepted: 15 August 2019

DOI: 10.1002/bmc.4685

RESEARCH ARTICLE

WILEY Biomedical Chromatography

Development and validation of an ultra-high-performance liquid chromatography–tandem mass spectrometry method to determine the bioavailability of warfarin and its major metabolite 7-hydroxy warfarin in rats dosed with oral formulations containing different polymorphic forms

Diaa Shakleya[1*] | Ziyaur Rahman[1,2] | Patrick J. Faustino[1*]

[1]Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

[2]Irma Lerma Rangel College of Pharmacy, Texas A&M Health Science Center, Texas A&M University, College Station, TX, USA

Correspondence
Patrick J. Faustino, Division of Product Quality Research, Office of Testing and Research, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993, USA.
Email: patrick.faustino@fda.hhs.gov

Abstract

A simple, sensitive and rapid ultra-high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry method was developed and validated for the quantification of warfarin and 7-hydroxy warfarin in Sprague Dawley (SD) rats. Animals were administered a single dose of warfarin sodium formulations (crystalline and amorphous) at 12 mg/kg via oral gavage and blood was drawn over a 96-h time course. Sample process recoveries, matrix effect and analyte stability were determined. The linearity for warfarin and 7-hydroxy warfarin was from 5 to 2000 ng/mL in blank SD rat plasma. Correlation coefficients (r^2) for standard calibration curves were >.98 and analytes quantified within ±15% of target at all calibrator concentrations. The average percent accuracy and precision for intra- and inter-day were 93.7%–113.8% and ≤12.1%, respectively, for warfarin and 7-hydroxy warfarin, across the quality control standards (5, 10, 500, 1800 and 2000 ng/mL). Acceptable analytical recovery (>55%) was achieved with process efficiencies >41.5% and matrix effects <139.9% over the analytical range. Both analytes were stable in stock solution, autosampler, benchtop and three cycles of freeze-thaw with percent accuracy ≥90.2% and precision (percent relative standard deviation) ≤14%. The validated method was successfully applied to a pre-clinical bioavailability study of crystalline and amorphous warfarin sodium formulations in SD rats.

KEYWORDS

7-hydroxy warfarin, amorphous, bioavailability, crystalline, LC-ESI-MS/MS, warfarin

1 | INTRODUCTION

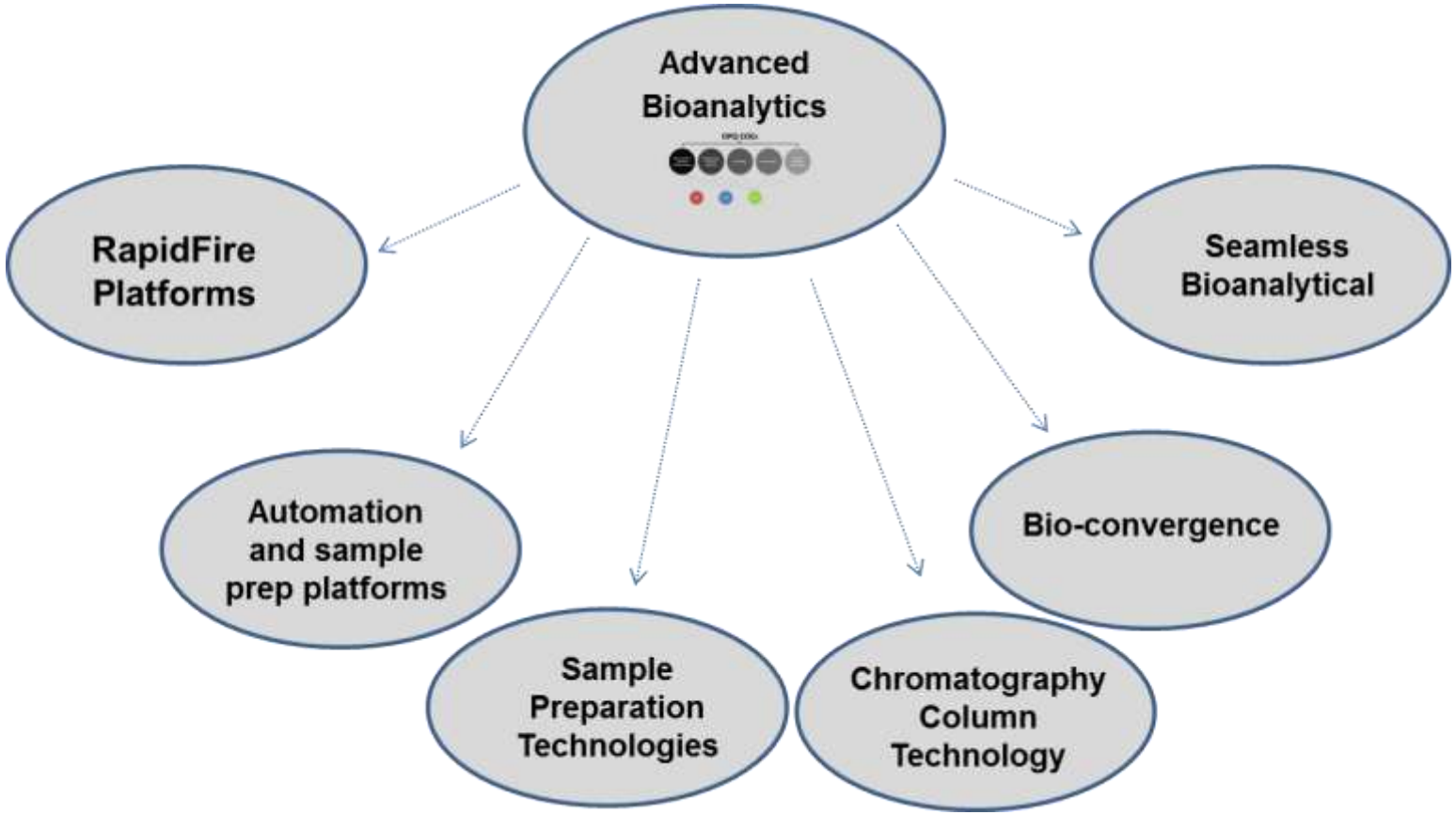
Warfarin sodium is an anticoagulant that was first approved by the US Food and Drug Administration (FDA) in 1954 (Porter, 2010) under the brand name Coumadin. According to the drug watch online publication, warfarin is one of the original anticoagulant medications, also referred to as a blood thinner. It is used clinically to prevent strokes and other serious complications associated with atrial fibrillation, a condition resulting in an irregular heart rate (Compton, 2018).

The drug product contains a racemic mixture of warfarin *R* and *S* enantiomers and is formulated as an isopropanol crystalline clathrate.

*The scientific publication reflects the views of the authors and should not be construed to represent FDA's views or policies.

Advanced Bioanalytics

- **Innovation Platforms for Bioanalysis**

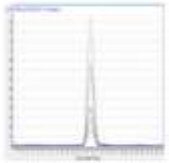


Advanced Bioanalytics

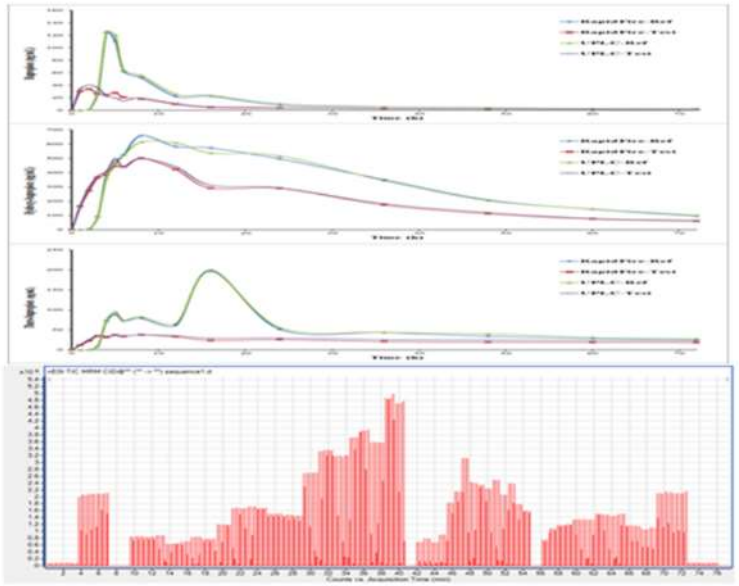
- **Advanced BioAnalytics**

Innovative Promise-"Rapid Fire" Analytics

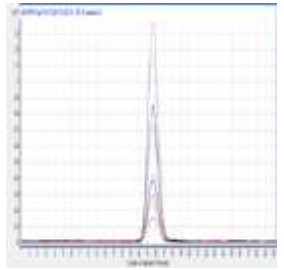
- *Innovative Promise, Transform clinical studies*
  - *Agilent RapidFire MS/MS*
    - Micro-robotic sampling
    - No chromatographic interface
    - On-line sample cleanup
    - Sample analysis times of 7-20 seconds
  - Advance regulatory biopharmaceutics

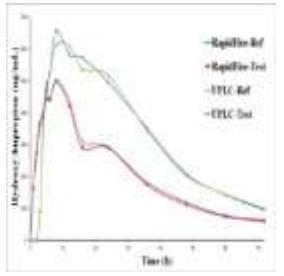


Clinical Bioequivalence Study-Bupropion



Rapid Fire BE data was shown to nearly match the previous regulatory study bupropion BE patient data and it was also shown to be Rapid Fast!

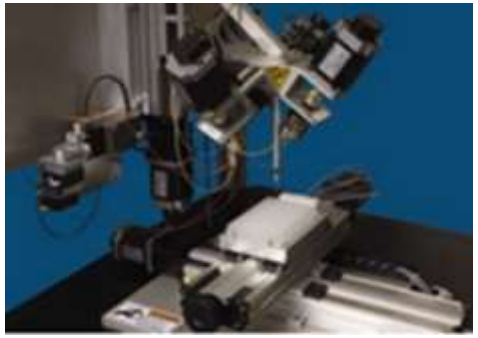




Summary

- The FDA Bioanalytical Method Validation Guidance is a foundational document

- The history of the guidance (workshop reports) highlights the advancement of the regulatory science of bioanalytical method validation
- The FDA works with sponsors, regulators and academia to translate the regulatory science of bioanalytical method validation
- Innovation and the next technological steps for bioanalytics will challenge/advance the guidance
- Thank you for participating!



Acknowledgements

- The Workshop Organizing Committee
- Dr. Larry (Sau) Lee and Dr. Thomas O’Connor
- Drs Shakleya, Zhang and Wang
- Dr. Sam Haidar
- Dr. Dasgupta, Ayala, Bonapace and Kassim
- Dr. Celia Cruz and Dr. Mansoor Khan (Advanced Analytics)
- Dr. Vinod Shah and Dr. Ajaz Hussain
- **Dr. Brian Booth-Agency POC for ICH M10**

Workshop Session

- **Regulated Bioanalysis Workshop: Current Requirements and Expectations**
  - **Office of Pharmaceutical Quality (OPQ) "*Guidance and laboratory perspectives*"**

  - **Presentation 1 (9:15-9:35AM)**
    - *Bioanalytical Method Validation: History, Process, and Regulatory Perspectives (BMV) Guidance*-Dr. Patrick Faustino

  - **Presentation 2 (9:35-9:55AM)**
    - *Regulated Bioanalysis for Large Molecules*-Dr. Jinhui Zhang

  - **Presentation 3 (9:55-10:15AM)**
    - *Regulated Bioanalysis for Small Molecules*-Dr. Diaa Shakleya

  - **Q & A Discussion (10:15-10:30AM)**
    - *Science based perspectives for the application of the BMV*