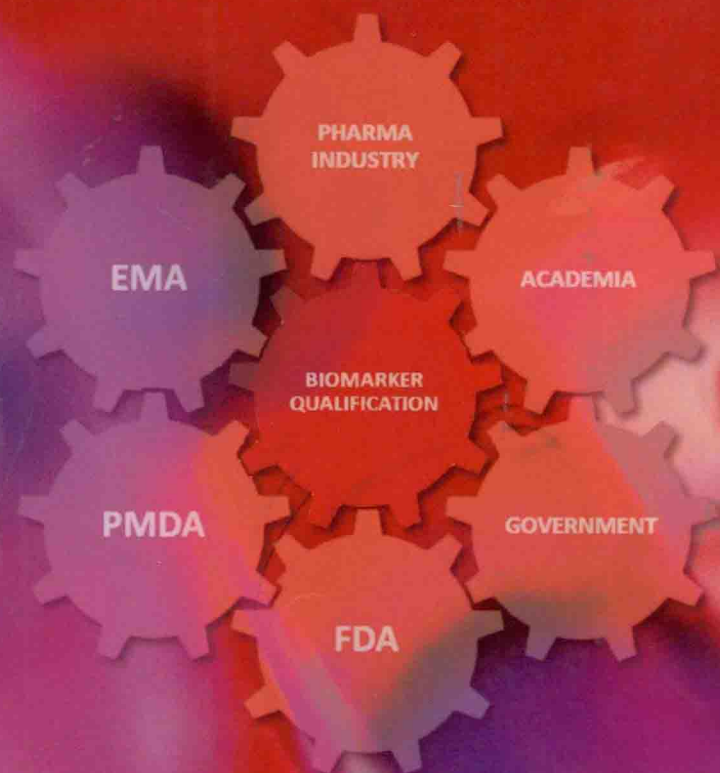
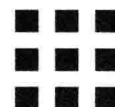


Federico Goodsaid  
William B. Mattes



# The Path from Biomarker Discovery to Regulatory Qualification





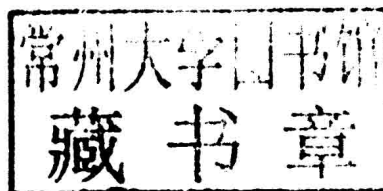
# The Path from Biomarker Discovery to Regulatory Qualification

Federico Goodsaid

*Strategic Regulating Intelligence, Regulatory Affairs, Vertex  
Pharmaceuticals, Washington DC, USA*

William B. Mattes

*PharmPoint Consulting, Poolesville, Maryland, USA*



Amsterdam • Boston • Heidelberg • London  
New York • Oxford • Paris • San Diego  
San Francisco • Singapore • Sydney • Tokyo

Academic Press is an imprint of Elsevier



Academic Press is an imprint of Elsevier  
The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK  
225 Wyman Street, Waltham, MA 02451, USA

Copyright © 2013 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced, stored in a retrieval system or transmitted in any form or by any means electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the publisher. Permissions may be sought directly from Elsevier's Science & Technology Rights Department in Oxford, UK: phone (+44) (0) 1865 843830; fax (+44) (0) 1865 853333; email: [permissions@elsevier.com](mailto:permissions@elsevier.com). Alternatively, visit the Science and Technology Books website at [www.elsevierdirect.com/rights](http://www.elsevierdirect.com/rights) for further information

#### **Notice**

No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein. Because of rapid advances in the medical sciences, in particular, independent verification of diagnoses and drug dosages should be made

#### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library

#### **Library of Congress Cataloging-in-Publication Data**

A catalog record for this book is available from the Library of Congress

ISBN : 978-0-12-391496-5

For information on all Academic Press publications  
visit our website at [elsevierdirect.com](http://elsevierdirect.com)

Typeset by TNQ Books and Journals  
[www.tnq.co.in](http://www.tnq.co.in)

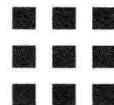
Printed and bound in the United States of America

13 14 15 16 17 10 9 8 7 6 5 4 3 2 1



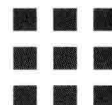
Working together  
to grow libraries in  
developing countries

[www.elsevier.com](http://www.elsevier.com) • [www.bookaid.org](http://www.bookaid.org)



# The Path from Biomarker Discovery to Regulatory Qualification





# Contributors

**Shashi Amur**

Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, USA

**Jiri Aubrecht**

Pfizer Inc., Groton, Connecticut, USA

**Joseph V. Bonventre**

Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA

**Bruce D. Car**

Pharmaceutical Candidate Optimization, Bristol-Myers Squibb, Inc., Princeton, New Jersey, USA

**Jean-Philippe Couderc**

University of Rochester Medical School, Rochester, New York, USA

**Daniel C. Danila**

Department of Medicine, Weill Cornell Medical College, New York, USA

**Frank Dieterle**

Novartis Pharma AG, Basel, Switzerland

**Stephen T. Furlong**

Astra Zeneca, Wilmington, Delaware, USA

**Federico Goodsaid**

Strategic Regulatory Intelligence, Regulatory Affairs, Vertex Pharmaceuticals, Washington DC, USA

**Ernie Harpur**

Institute of Cellular Medicine, Newcastle University, Newcastle, UK

**Akihiro Ishiguro**

PMDA Omics Project (POP), Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

**Jeffrey Jacob**

Cancer Prevention Pharmaceuticals and Critical Path Institute, Tucson, Arizona, USA

**Peter G. Lord**

DiscoTox Ltd., Hebden Bridge, West Yorkshire, UK

**William B. Mattes**

PharmPoint Consulting, Poolesville, Maryland, USA

**Raegan O'Lone**

HESI, Washington DC, USA

**Yasuto Otsubo**

PMDA Omics Project (POP), Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

**Syrl Pettit**

HESI, Washington DC, USA

**Donald G. Robertson**

Pharmaceutical Candidate Optimization, Bristol-Myers Squibb, Inc., Princeton, New Jersey, USA

**Denise Robinson-Gravatt**

Pfizer Inc., Groton, Connecticut, USA

**Howard I. Scher**

Memorial Sloan-Kettering Cancer Center, New York, USA

**John R. Senior**

Associate Director for Science, Food and Drug Administration (FDA), Silver Spring, Maryland, USA

**Yoshiaki Uyama**

PMDA Omics Project (POP), Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan

**Vishal S. Vaidya**

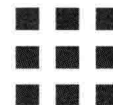
Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; Harvard School of Public Health, Boston, Massachusetts, USA

**Spiros Vamvakas**

Head of Scientific Advice, European Medicines Agency, London, UK

**Stephen A. Williams**

Somatologic Inc., Boulder, Colorado, USA



# Preface

Successful work on drug development and regulatory review is often associated with strictly normative thinking. Drug development paths and regulatory policy can reach a level of acquiescence where the science which should drive these is only marginally integrated in them. The result of this process is drug development which yields less useful and less new drugs and regulatory review which mirrors and exacerbates the weaknesses of drug development.

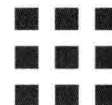
The use of biomarkers in drug development at all levels is a powerful link to the science responsible for the identification, development and testing for transformative therapies. Whether in the assessment of drug safety or drug efficacy, in early or late development, in patient selection and characterization, and within a broad range of analytical platforms, biomarkers provide the information with which industry and regulators can determine whether a drug is safe and efficacious. While conventional definitions seek increasingly tenuous classifications for biomarkers, their shared value continues to be in what these biomarkers tell us about a drug and about what a drug can or cannot do in patients which should benefit from it. Results from biomarker measurements are not necessarily normative, and their inclusion in evolving concepts about why and when a drug is safe and efficacious continuously reminds us that we will only succeed with new therapies if we fully understand this information and the science behind it.

The collection of papers in this book includes contributions from scientists in academic institutions, pharmaceutical companies and regulatory agencies who have worked and continue to work on the best way to develop and use biomarkers from both the perspective of the critical path for drug development as well as from the perspective of the integration of these biomarkers in regulatory review. We hope that this snapshot of work carried out over the past decade will encourage further discussion about novel biomarkers and about how – and when – to make the best use of these powerful tools.

Federico Goodsaid and William B. Mattes







# Contents

Contributors xi

Preface xiii

## Section 1 Introduction

1. Biomarker Applications in the Pharmaceutical Industry	3
<i>William B. Mattes</i>	
Diagnostic Applications	7
Prognostic Applications	10
Intervention Management/Monitoring	12
Concluding Remarks	14
2. Impact of Biomarker Qualification Regulatory Processes on the Critical Path for Drug Development	21
<i>Federico Goodsaid</i>	
Introduction	21
Has the Process at the FDA (CDER) Achieved the Goals Originally Proposed by the Pharmacogenomics Guidance in 2005 and the Critical Path Opportunities List and Report in 2006?	22
What are the Strengths and Weaknesses of the Different Versions of a Biomarker Qualification Process Developed in Each ICH Region?	26
How Well Have the Different Versions of This Process Been Harmonized across These Regions?	30
What are the Opportunities and Challenges for a Single, Universal, Biomarker Qualification Process?	30
How Can We Develop Metrics with Which to Measure the Impact of These Processes on Drug Development and Their Acceptance by the Pharmaceutical Industry?	31
Summary	32

3. Regulatory Experience of Biomarker Qualification in the EMA <i>Spiros Vamvakas</i>	35
Other Informal Interactions with the EMA	36
Examples of Qualification Opinions	37
4. Regulatory Experience at the FDA, EMA, and PMDA <i>Akihiro Ishiguro, Yasuto Otsubo, Yoshiaki Uyama</i>	41

## Section 2 Biomarker Development and Qualification in the Pharmaceutical Industry

5. The Impact of Changing Context of Use on Weight of Evidence for Qualification of Biomarkers: A Case Study in Ischemic Stroke <i>Stephen A. Williams</i>	47
6. Safety Biomarker Development and Qualification in the Pharmaceutical Industry <i>Stephen T. Furlong</i>	53
7. First-Ever Regulatory Biomarker Qualification – Review and Insights by a Participant <i>Frank Dieterle</i>	59
8. Metabolomics-Derived Biomarkers of Drug-Induced Skeletal Muscle Injury and Urinary Bladder Transitional Cell Carcinoma in Rats <i>Bruce D. Car, Donald G. Robertson</i>	67
Metabolomic Biomarker for Drug-Induced Skeletal Muscle Injury in Rats	67
Metabolomic Biomarker for Causation of Bladder Tumorigenesis in Rats	68
Summary	69
9. Molecular Biomarkers for Patients with Castration-Resistant Prostate Cancer: Validating Assays Predictive of Tumor Response <i>Daniel C. Danila, Howard I. Scher</i>	71
Unmet Needs to be Addressed with Biomarkers	71

FDA-Approved Method and Demonstrated Use	72
Emerging Molecular Biomarkers	73
Validating Genomic Biomarkers in CTCs	74
Molecular Biomarkers in a CLIA-Certified Laboratory	76
Changing the Paradigm for Assessment of Recurrent Prostate Cancer: a Liquid Biopsy	76

### Section 3 Toxicogenomic Biomarkers

10. Gene Logic and Toxicogenomics Biomarkers <i>William B. Mattes</i>	83
11. The When, Where and How of Toxicogenomic Submissions to Regulatory Agencies <i>Peter G. Lord</i>	91
Introduction and Background	91
Toxicogenomic Applications in Drug Discovery and Development	92
The Case Examples	93
A Hypothetical Submission in Support of the Safety Claims for a Hypolipidemic Drug	95
Highlights from the Discussions	95
Conclusions	99
12. Biomarker Qualification – Past, Present and Future <i>Denise Robinson-Gravatt, Jiri Aubrecht, Raegan O’Lone, Syril Pettit</i>	101
HESI’s Contributions to the Emerging Field of Toxicogenomics	102
Use of Toxicogenomics to Biological Assess Mechanisms – Case Studies	103
Current Focus and Activities of the HESI Genomics Committee	105
Summary and Future Horizons	106

### Section 4 Biomarkers of Drug Safety

13. ‘Classic’ Biomarkers of Liver Injury <i>John R. Senior</i>	111
Bilirubin	111

Alternative and Discarded Biomarkers	117
Aminotransferases (Transaminases)	118
Combined ALT and TBL Measurements	120
Conclusions and Recommendations	123
<b>14. Qualification of Urinary Biomarkers for Kidney Toxicity</b>	<b>129</b>
<i>Joseph V. Bonventre, Vishal S. Vaidya</i>	
Regulatory Framework: Advancing the Science of Biomarkers	129
Kidney Injury Molecule-1: Characteristics	130
Collaborations in Consortia	131
Interactions with the FDA and EMA	132
Translation to Clinical Use	134
Conclusions	135
<b>Section 5 Consortia</b>	
<b>15. Renal Biomarker Qualification: An ILSI Health and Environmental Sciences Institute Perspective</b>	<b>141</b>
<i>Sybil Pettit, Ernie Harpur</i>	
Safety Biomarker Research – the Origin of this Activity in HESI	141
Creation of Biomarker Working Groups	143
Biomarkers of Nephrotoxicity Committee (BNC)	143
Biomarker Qualification: the Changing Landscape	146
<b>16. Vignette Regarding Consortia: C-Path Institute</b>	<b>149</b>
<i>Jeffrey Jacob</i>	
<b>17. The Telemetric and Holter ECG Warehouse to Enable the Validation and Development of Novel Electrocardiographic Markers</b>	<b>153</b>
<i>Jean-Philippe Couderc</i>	
Introduction	153
QT Interval as a Safety Marker in Drug Development	154
QT Interval: from a Biomarker to a Surrogate Marker	155
The Thorough QT Studies (TQT)	157

Improving the QT Marker	158
QT, Heart Rate and Autonomic Regulation	159
Inception of the Telemetric and Holter ECG Warehouse (THEW): a Model to Develop Academia-Regulators-Industries Partnerships	160
Involving the FDA and Industry	161
Participation by the National Institutes of Health	162
Facilitating the Submission of New ECG Markers to the FDA	162
Conclusions and Perspectives	163

## Section 6 Path to Regulatory Qualification Process Development

18. Path to Regulatory Qualification Program Development: A US FDA Perspective <i>Shashi Amur</i>	169
The Biomarker Qualification Process at US FDA	170
Current Status of Biomarker Qualification Submissions	171
Future Perspectives	172
19. Path to Regulatory Qualification Process Development <i>Yasuto Otsubo, Akihiro Ishiguro, Yoshiaki Uyama</i>	175
20. The Tortuous Path From Development to Qualification of Biomarkers <i>Federico Goodsaid</i>	179
Index	181



SECTION

1



# Introduction



