

INJECTABLE DRUG DEVELOPMENT

TECHNIQUES TO REDUCE PAIN AND IRRITATION

Edited by

Pramod K. Gupta

and

Gayle A. Brazeau

Interpharm Press
Denver, Colorado



Invitation to Authors



Interpharm Press publishes books focused upon applied technology and regulatory affairs impacting healthcare manufacturers worldwide. If you are considering writing or contributing to a book applicable to the pharmaceutical, biotechnology, medical device, diagnostic, cosmetic, or veterinary medicine manufacturing industries, please contact our director of publications.

Library of Congress Cataloging-in-Publication Data

Injectable drug development : techniques to reduce pain and irritation /
edited by Pramod K. Gupta and Gayle A. Brazeau.
p. cm.

Includes bibliographical references and index.

ISBN 1-57491-095-7

1. Injections. 2. Injections—Complications. 3. Drug development.

I. Gupta, Pramod K., 1959— . II. Brazeau, Gayle A.

[DNLM: 1. Injections—adverse effects. 2. Pain—chemically induced.

3. Pain—prevention & control. 4. Pharmaceutical Preparations—
administration & dosage. WB 354 156 1999]

RM169.I49 1999

615'.6—dc21

DNLM/DLC

for Library of Congress

99-26911

CIP

10 9 8 7 6 5 4 3 2 1

ISBN: 1-57491-095-7

Copyright © 1999 by Interpharm Press. All rights reserved.

All rights reserved. This book is protected by copyright. No part of it may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without written permission from the publisher. Printed in the United States of America.

Where a product trademark, registration mark, or other protected mark is made in the text, ownership of the mark remains with the lawful owner of the mark. No claim, intentional or otherwise, is made by reference to any such marks in this book.

While every effort has been made by Interpharm Press to ensure the accuracy of the information contained in this book, this organization accepts no responsibility for errors or omissions.

Interpharm Press
15 Inverness Way E.
Englewood, CO 80112-5776, USA

Phone: +1-303-662-9101
Fax: +1-303-754-3953
Orders/on-line catalog:
www.interpharm.com



BIONE S
WB
354
I56
1999

Contents

Preface	xiii
Acknowledgments	xiv
Editors and Contributors	xv

A: BACKGROUND OF PAIN, IRRITATION, AND/OR MUSCLE DAMAGE WITH INJECTABLES

1. Challenges in the Development of Injectable Products	3
<i>Michael J. Akers</i>	
General Challenges	4
Safety Concerns	5
Microbiological and Other Contamination Challenges	6
Stability Challenges	8
Solubility Challenges	10
Packaging Challenges	11
Manufacturing Challenges	11
Delivery/Administration Challenges	13
References	14

iv	<i>Injectable Drug Development</i>	
2.	Pain, Irritation, and Tissue Damage with Injections	15
	<i>Wolfgang Klement</i>	
	Must Injections Hurt?	15
	Mechanisms of Pain and Damage	16
	Routes of Drug Injection	18
	<i>Cutaneous/Subcutaneous Injections</i>	18
	<i>Intramuscular Injections</i>	22
	<i>Intra-arterial Injections</i>	24
	<i>Intravenous Injections</i>	26
	Conclusions and Perspectives	49
	Acknowledgements	50
	References	50
3.	Mechanisms of Muscle Damage with Injectable Products	57
	<i>Anne McArdle and Malcolm J. Jackson</i>	
	Abstract	57
	Introduction	57
	Mechanisms of Muscle Damage	58
	<i>Elevation of Intracellular Calcium Concentration</i>	58
	<i>Increased Free Radical Production</i>	60
	<i>Loss of Energy Homeostasis</i>	61
	Methods of Assessing Drug-Induced Skeletal Muscle Damage	62
	<i>Microscopic Analysis of Skeletal Muscle</i>	62
	<i>Muscle Function Studies</i>	63
	<i>Leakage of Intramuscular Proteins</i>	64
	<i>Microdialysis Studies of Individual Muscles</i>	64
	<i>Cellular Stress Response</i>	65
	Techniques to Assess the Mechanisms of Muscle Damage	66
	<i>Models of Muscle Damage</i>	66
	<i>Techniques to Show Changes in Muscle Calcium Content</i>	66
	<i>Markers of Increased Free Radical Activity</i>	67
	<i>Methods of Measuring Cellular Energy Levels</i>	67
	Conclusions	67
	Acknowledgments	67
	References	68

**B: METHODS TO ASSESS PAIN, IRRITATION, AND
MUSCLE DAMAGE FOLLOWING INJECTIONS**

4. In Vitro Methods for Evaluating Intravascular Hemolysis	77
<i>Joseph F. Krzyzaniak and Samuel H. Yalkowsky</i>	
Significance	78
In Vitro Methods for Evaluating Hemolysis	79
<i>Static Methods</i>	81
<i>Dynamic Methods</i>	82
Comparison of In Vitro and In Vivo Hemolysis Data	85
Summary of In Vitro Methods	86
References	87
 5. Lesion and Edema Models	 91
<i>Steven C. Sutton</i>	
Edema and Inflammation	91
Lesion Models	92
<i>Rabbit</i>	92
<i>Mice</i>	96
<i>Rat</i>	96
Biochemical Models	97
<i>Serum Glutamic-Oxaloacetic Transaminase</i>	97
<i>N-Acetyl-β-Glucosaminidase</i>	97
<i>Myeloperoxidase</i>	97
<i>Creatine Kinase</i>	98
Edema Models	105
<i>Inducing Edema</i>	105
<i>Exudative Models of Inflammation</i>	105
<i>Vascular Permeability Models</i>	105
<i>Footpad Edema Models</i>	106
Correlation of Models	107
<i>Rabbit Lesion Versus Rabbit Hemorrhage Score Model</i>	107
<i>Rabbit Lesion Versus Rabbit CK Model</i>	108
<i>Rabbit Lesion Versus Rat Footpad Edema Model</i>	109
<i>Rabbit Lesion Versus Rat CK Model</i>	109
<i>Rat and Human</i>	110

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.